Postgraduate Medicine

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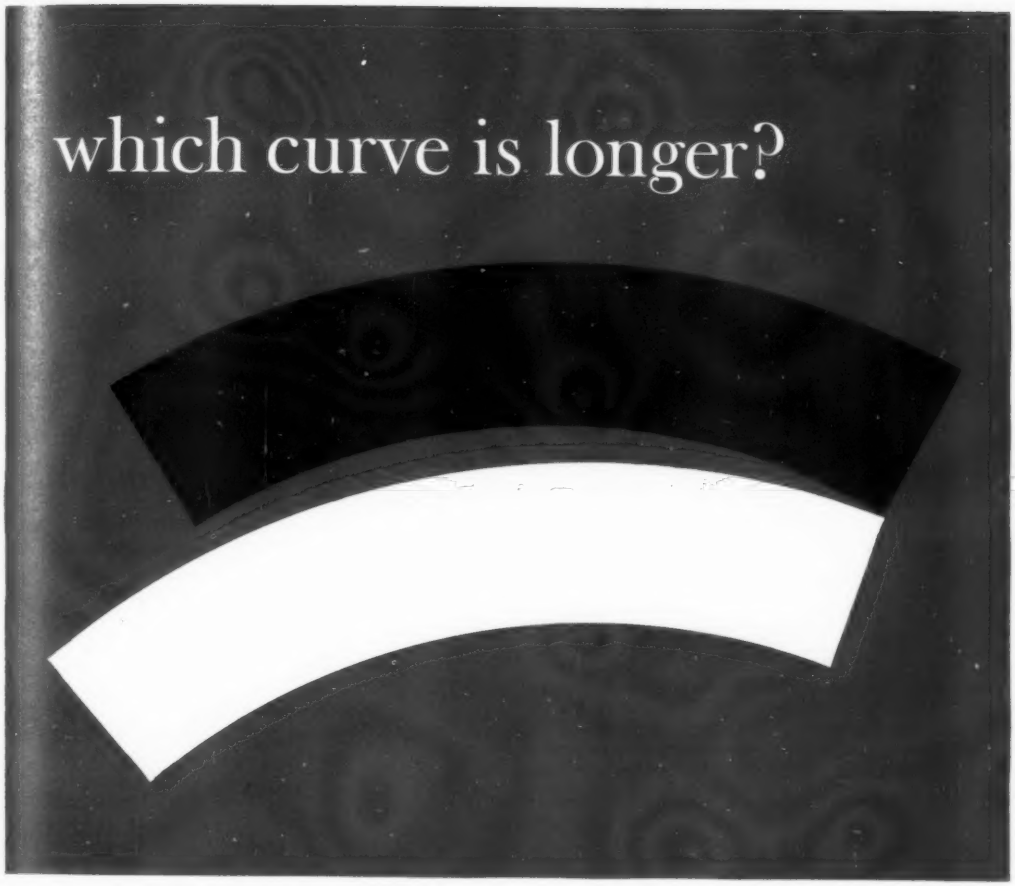

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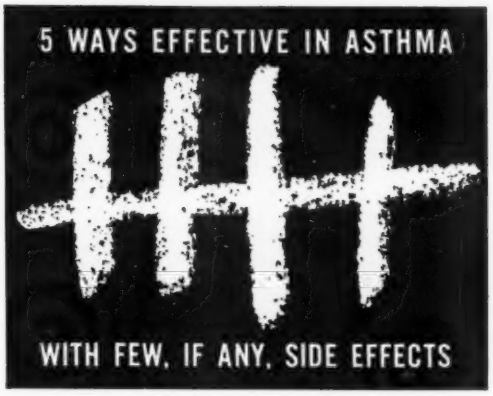

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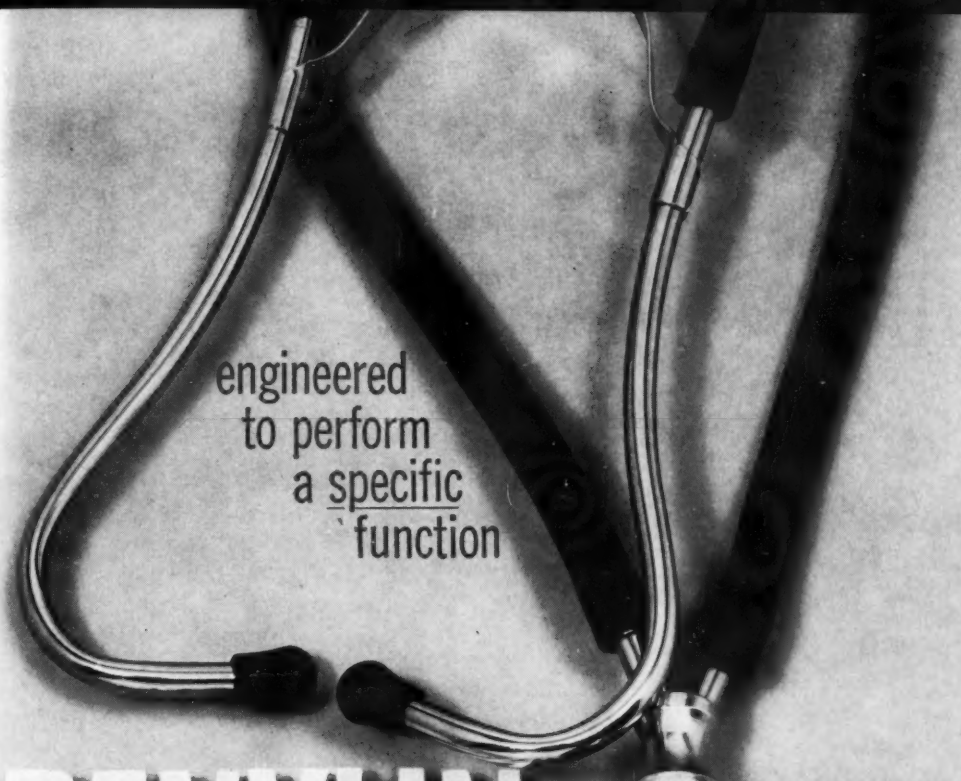

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Problems and Solutions

Readers are invited to submit questions relating to problem cases. Inquiries will be answered by qualified consultants and replies forwarded by mail immediately. Selected problems and solutions are published each month in this section.

• BLACK, HAIRY TONGUE

P. What causes melanotrichia linguae (black, hairy tongue), and how should this condition be treated?

M.D.—Illinois

S. Black, usually hairy tongue involves keratotic enlargement of the filiform papillae, a process which entraps color-forming bacteria, yeasts, decaying food particles, food pigments, and, frequently, tobacco stains; melanin is not present in unusual amounts. The causes initiating the process are as yet undetermined, but the use of antibiotic agents (medically or in food), the presence of an acidic oral environment, and the aforementioned bacteria and yeasts have been implicated.

Methods of treatment which apparently have achieved good, lasting results include applications of dequalinium chloride or podophyllum resin, alkalinization of the mouth, mechanical cleansing, the application of pancreatin, and painting with cresyl violet.

Details of each method can be found in the following references: (1) Winer, L. H.: Black hair tongue: A comparative study of black hair tongue, geographic tongue, and drug eruption of the tongue. A. M. A. Arch. Dermat. 77:97-103 (January) 1958; (2) Lineback, M.: The biocenologic approach to black hairy tongue with new concepts of its treatment: Secondary mycosis linguae of pathologic significance. Laryngoscope 69:1194-1212 (September) 1959; and (3) Stockdale, C. R. and Banks, L. L.: The treatment of black hairy tongue with dequalinium chloride: A preliminary report. Practitioner 182: 215-217 (February) 1959.

• OCCIPITAL FOLLICULITIS

P. A 28 year old Negro man with occipital folliculitis has failed to respond to manual epilation of infected follicles or to treatment with antibiotic ointments and creams and hexachlorophene soaps. Local application of steroids has not been helpful. Urinalysis yielded negative results for sugar.

What treatment would you suggest? Is systemic antibiotic therapy indicated?

M.D.—Pennsylvania

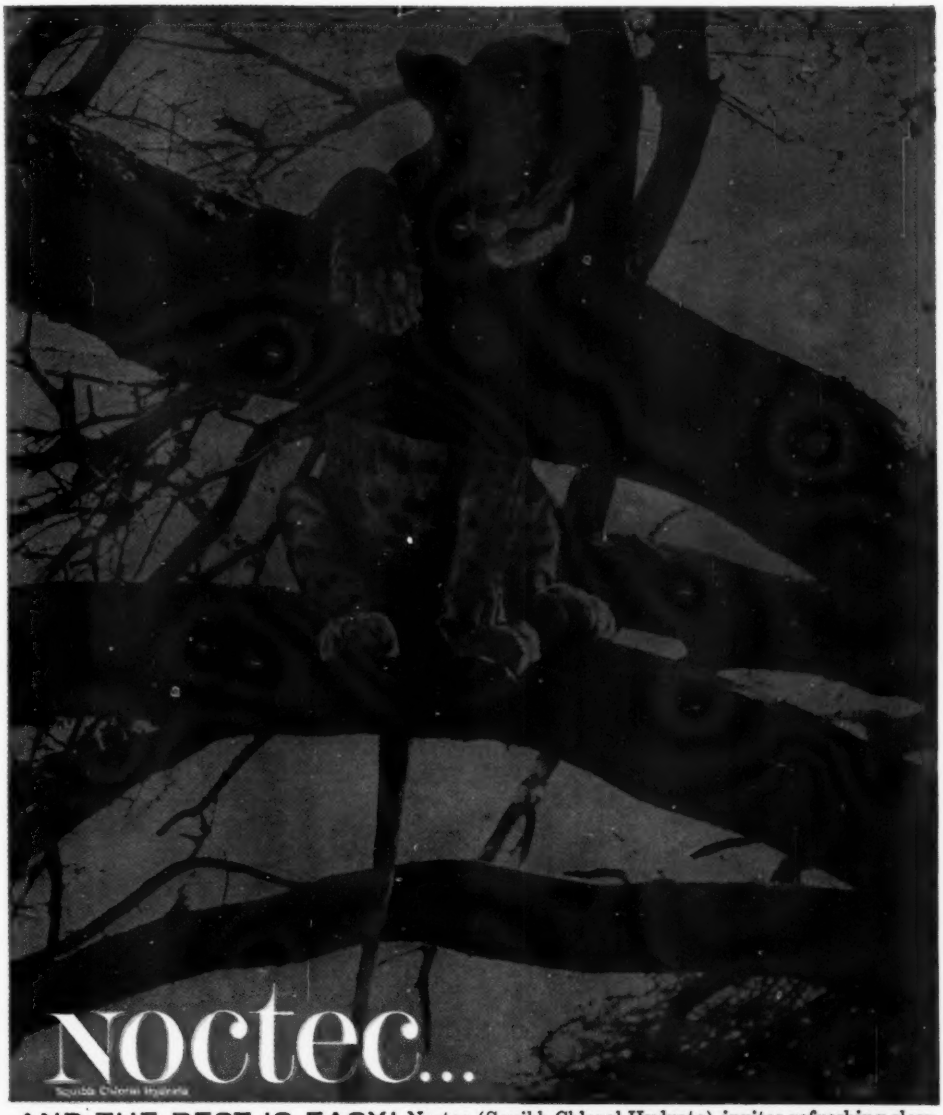
S. Occipital folliculitis in the Negro is a part of or leads to the condition known as folliculitis keloidalis. Many organisms have been isolated in this condition, and these are not constant.

Continued manual epilation of retained hairs and drainage of abscesses are important. Sensitivity studies of the organisms present should be done, and, where possible, the antibiotic agent or agents indicated by these studies should be applied. These agents have been found to be more effective in a lotion than in an ointment.

Warm wet packs of 1:5000 ZEPHIRAN® chloride or 1:30 Vleminckx solution applied for one-half hour three times daily should be helpful. When scarring is already present, treatment with carbon dioxide slush (sulfur, acetone powder and dry ice) can be very beneficial in certain cases. X-ray therapy used cautiously should help. Systemic antibiotic agents are rarely used to treat this condition; however, if the sensitivity studies indicate that the organisms are sensitive to orally administered antibiotic agents, a trial is in order.

Since this type of condition is stubborn, treatment requires the cooperation of the patient.

(Continued on page A-18)



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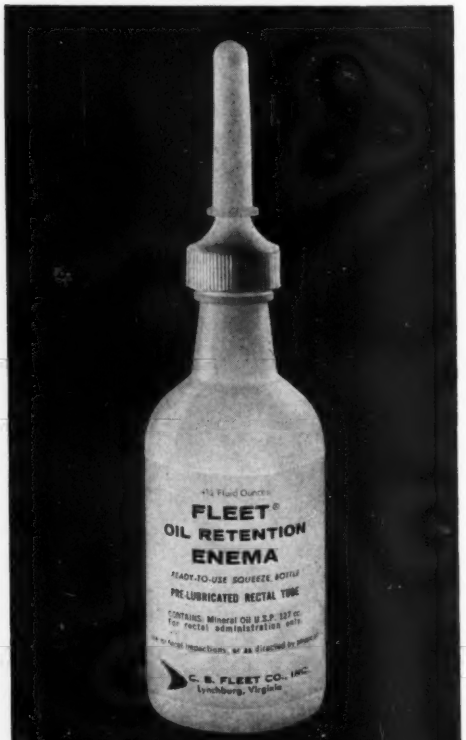

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• URETHRITIS FOLLOWING INSTRUMENTATION

P. What treatment do you suggest for urethritis resulting from instrumentation such as cystoscopy or dilatation by urethral sounds? This refers especially to situations in which the only symptom is persistent soreness either with a nonpurulent, serosanguineous discharge or without discharge or infection.

M.D.—Colorado

S. If no stricture of the urethra is present and if no symptoms or findings suggest infection or inflammation of the prostate gland, I would recommend the use of sitz baths with a mild antiseptic and, after one week, massage of the prostate gland. Some patients who are hypersensitive to instrumentation and the resulting mild irritation frequently will recover without active treatment. Soreness and discharge are usually secondary to nonspecific, asymptomatic inflammation of the prostate gland.

• ADENOMATOUS POLYPS OF THE DUODENUM

P. In a 46 year old man with symptoms of duodenal ulcer, a study of the upper gastrointestinal tract revealed filling defects of the duodenum. A diagnosis of adenoma or duodenitis was made, and the patient was treated conservatively for three weeks. A second x-ray examination at this time again demonstrated the filling defects. Following pathologic studies, a diagnosis of multiple adenomatous polyps of the duodenum was made, and partial duodenectomy was done.

At the present time, approximately 10 months after the operation, the patient is experiencing heartburn and epigastric distress. Further development of polypoid defects in the duodenum, close to or involving the ampulla, is evident on x-ray examination. Results of liver function tests are normal.

In the absence of obstruction, what would be the best treatment for this condition?

M.D.—Oregon

S. I have never seen a patient with multiple adenomatous polyps of the duodenum. I suggest that the slides be sent to several pathologists for evaluation. If the diagnosis is substantiated, the case should be reported in the literature, because it is of unusual interest. In the absence of malignancy, additional surgery should not be done.

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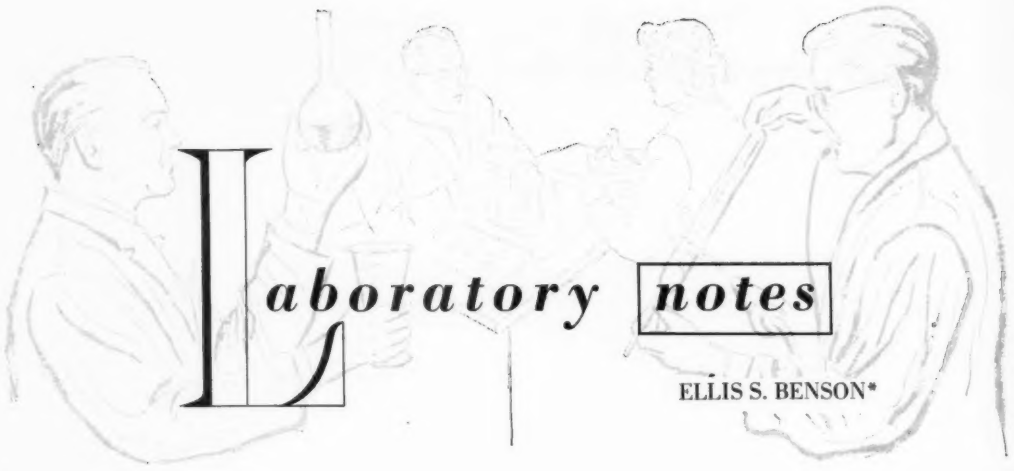

Laboratory notes

ELLIS S. BENSON*

Pure Water, Part 2

DOUGLAS A. NELSON†

University of Minnesota Medical School, Minneapolis

EVERY laboratory has problems related to the purity of its water. The most elite analytic procedures in chemistry or in bacteriologic examination can come to grief through nothing more esoteric than contaminated water thought to be pure.

In last month's column, a description of two main methods of purification of water, distillation and de-ionization, included consideration of their limitations and relative efficiency. This discussion includes common contaminants of supposedly purified water, their detection, and difficulties which they may cause.

Criteria for maximal levels of contaminants are given in "The Pharmacopoeia of the United States of America"[1] and have been listed by the American Chemical Society.[2] These levels may be unsuitable for certain critical purposes; then, special attention must be given to removal of such contaminants. Methods for quantitating most contaminants have been described by the American Public Health Association[3] and others.

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology; †Instructor in Laboratory Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

Common Contaminants in Supposedly Purified Water

Residual chlorine—Residual chlorine, which is frequently used for treating public water supplies, may be present as free chlorine or as various chloramines. A pure well with no organic matter will deviate negligible quantities of chlorine, while a polluted surface stream will require considerable amounts. Therefore, if the dosage and contact time for chlorination in such pretreatment are not properly adjusted for the nature of the raw water, it is possible that at times a public water supply could contain excessive amounts of residual chlorine.

It is not uncommon for distilled water to contain chlorine and hypochlorous acid in small but significant amounts. Chlorine can be detected and determined colorimetrically with orthotolidine,[3] and chloride is detected by adding silver nitrate to water acidified with

(Continued on page A-22)

FOUR HUNDRED MILLIGRAMS OF PURE

PAIN RELIEF

NEW

analexin®-400

400 milligrams of phenyramidol HCl

THE ONLY SIGNIFICANT RESPONSE IS RELIEF FROM PAIN

EXCEEDINGLY EFFECTIVE "... The 85.1% incidence of effectiveness with the 400 mg. dose has exceeded the analgesic effectiveness of any other analgesic agent which we have studied to date, either alone or in combination....The utilization of higher doses for short periods of time indicates that the medication has a large therapeutic range, and this is reflected in the high incidence of effectiveness and low likelihood of untoward reactions.

"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."[1]

EXTRAORDINARY MARGIN OF SAFETY. *Analexin-400 is non-narcotic and not narcotic related;* thus, it presents no danger of habituation or any other reaction associated with the frequent use of narcotics. Nor will Analexin-400 produce sedation, mental confusion or depression occasionally observed with other analgesics or interneuronal blocking agents.[1-23]

INDICATIONS: Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

DOSAGE: One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

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ANOTHER ACHIEVEMENT OF NEISLER RESEARCH **IRWIN, NEISLER & CO.** *75th year* DECATUR, ILLINOIS

nitric acid.[1] Investigating low and erratic results on standard solutions of uric acid, Caraway[4] found considerable free residual chlorine in his supply of distilled water. He found that 1 ppm of chlorine had significant inhibitory effects on the color development in uric acid determinations and also lowered the bilirubin values. The oxidizing action of free chlorine on hemoglobin can form appreciable concentrations of methemoglobin and also can decrease the stability of dilute standard solutions of sodium iodide which are used in determinations of protein-bound iodine. Determinations of phosphatase (the King-Armstrong method), inorganic phosphate (Fiske and Subbarow's method), glucose (Benedict's method), ammonia nitrogen (nesslerization), and protein (biuret test) were not significantly affected by 1 ppm of chlorine.[4]

Collier and Stuart[5] found unexpected interference with bacterial viability in suspensions of non-nutrient media, and traced the trouble to chloramines in their distilled water. Certain inadequacies in the still were allowing these substances to be steam-distilled over. It has been found that distilled water containing over 0.1 ppm of chlorine will completely inactivate biotin.[6]

Ammonia and organic matter—Nitrogen can be determined in several forms in some public water supplies, especially those whose source is surface water. Fluctuations in the amount of biologic waste products in the source waters may be so extreme that occasions arise when organic material escapes removal by the municipal water treatment plant. To detect this contamination, ammonia nitrogen can be measured by nesslerization directly or after distillation, or the different forms of nitrogen can be measured separately. Total organic matter can be estimated by the consumption of oxygen from permanganate.[3]

Because of the nonionic character of much of this material and its presence in even the best de-ionized water, it is essential to use good distilled water for procedures involving the determination of nitrogen.

Recently, in our own laboratory, the hemoglobins (done by the photometric oxyhemoglobin method) were found to be running approximately 1 gm. per cent low. The difficulty was traced to excess levels of organic matter and ammonia in the distilled water which presumably caused formation of alkaline hematin thus changing the spectroscopic characteristics of hemoglobin. The tap water was found to have an excessively high content of ammonia and organic matter at the time. Apparently, the still could not handle this load level at its ordinary rate of distillation.

Pyrogens—Pyrogens are bacterial products which cause fever when injected into the body. The most probable source of pyrogens in distilled water is carry-over by entrainment.[7] De-ionized water cannot be relied on to be free of pyrogens. Whittet[8] found, however, that many pyrogens could be removed by de-ionization and that the anion exchange resin was responsible for their removal. The "British Pharmacopoeia" and "The U. S. Pharmacopoeia" require that water for injection be prepared by distillation and that each batch be tested for pyrogens.

Freshly distilled water from three of 11 hospitals in the vicinity of Memphis was found by Swafford and Nobles[9] to contain pyrogens. All three had baffle plates or mechanical devices to prevent entrainment, and the measured conductivity was well within the accepted limits. In one, a leak was found in the condenser, allowing raw water to mix with the distillate. This experience indicates that ionic purity does not completely assure freedom from pyrogens.

Sterility—Distilled water is by nature sterile and becomes contaminated in the process of handling and storage. De-ionization will not remove colloidal or other nonionic impurities and is sterile only occasionally and by chance. The resin acts poorly as a bacterial filter, and, if not kept clean, it can lead to trouble due to bacterial contamination of the purified water. Eisman, Kull and Mayer[10] showed that the number of organisms in de-ionized water bears a direct relation to time elapsing between successive regenerations. Using raw water containing 50 bacteria per milliliter, they found that unit 1 of a resin, regenerated every three to four days, had an effluent con-

(Continued on page A-24)

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IN FRACTURE CASES

High levels of B and C vitamins are particularly important to quickly replenish vitamin reserves depleted by the stress of fractures. Such metabolic support with STRESSCAPS increases the chance for an uncomplicated convalescence.

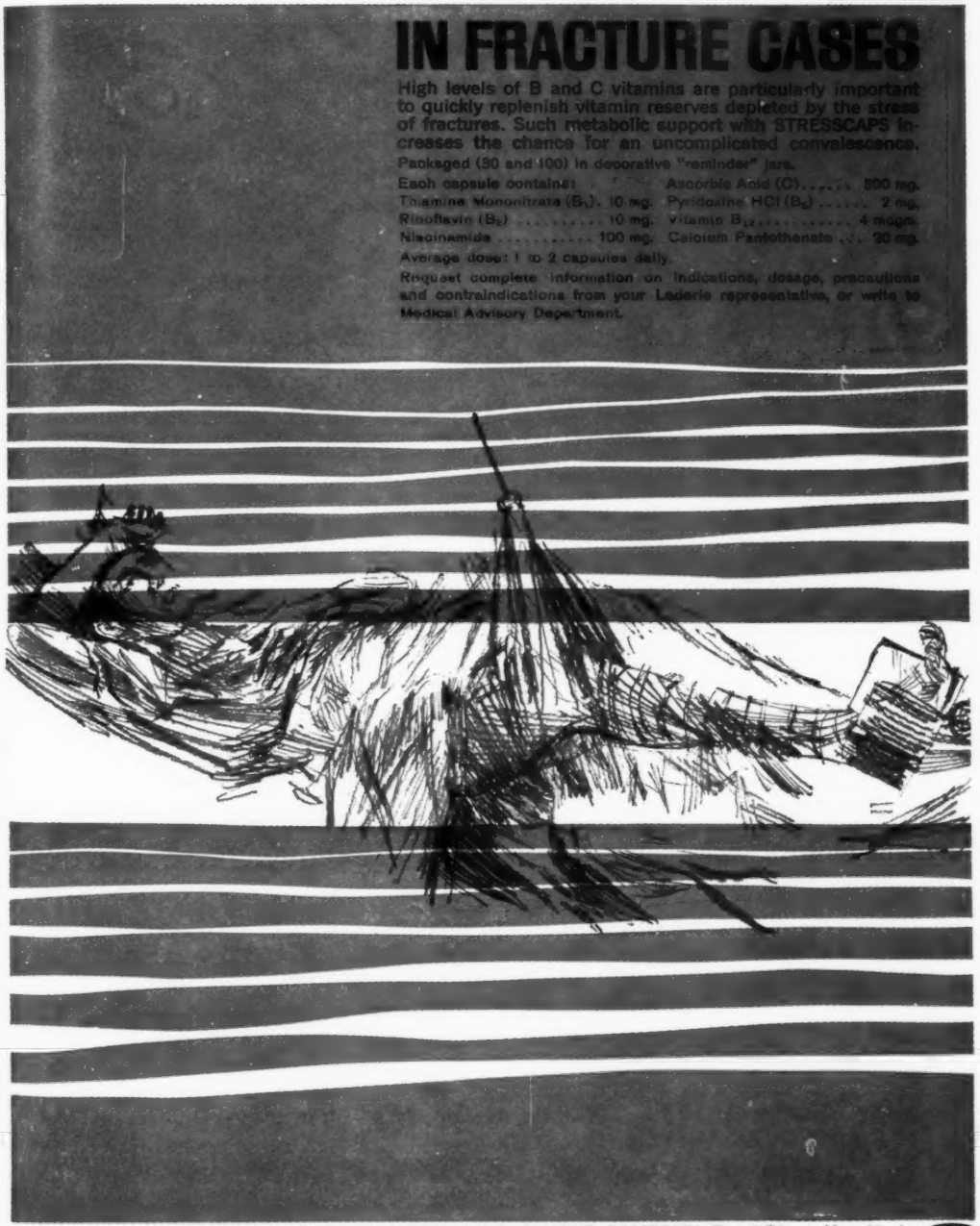
Packaged (30 and 100) in decorative "reminder" jars.

Each capsule contains:

Thiamine Mononitrate (B_1)	10 mg.	Ascorbic Acid (C)	500 mg.
Riboflavin (B_2)	10 mg.	Pyridoxine HCl (B_6)	2 mg.
Niacinamide	100 mg.	Vitamin B_{12}	4 mcgm.
		Calcium Pantothenate	20 mg.

Average dose: 1 to 2 capsules daily.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

TABLE 1

TRACE METAL CONTENT OF REDISTILLED AND ION EXCHANGE WATER BEFORE AND AFTER STORAGE*

SAMPLE	METAL CONCENTRATION (μG. PER 100 ML.)				
	Zn	*Pb*	*Cu*	*Fe*	*Al*
Barnstead water† redistilled in Pyrex	1.4	0.9	0.5	0.9	1.0
Stored in Pyrex bottle, two weeks	4.6	3.0	1.2	4.5	10.2
Stored in paraffin-lined bottle, two weeks	5.6	4.1	1.4	10.5	15.0
Barnstead water passed through mixed-bed ion exchange	0.5	0.5	0.5	0.5	1.0
Stored in polyethylene bag, two weeks	1.5	1.5	0.6	1.5	1.3

*From Healy, Morgan and Parker.[14]
†Water passed through a Barnstead metal still.

taining one organism per milliliter, whereas the effluent of unit 2, regenerated every 20 days, contained 6000 to 12,000 organisms per milliliter in spite of an acceptable chemical purity.

Carbon dioxide—Carbon dioxide rapidly enters pure water on its exposure to air, lowering the pH and increasing the conductivity. Free carbon dioxide in water may contribute to the corrosion of iron, copper or galvanized steel pipes, causing traces of iron, copper or zinc to appear in the water.[11]

Trace metals—Trace metals remaining after the purification of water can be exceedingly troublesome in work which demands water of the highest purity.

The need for large quantities of low-cost water, free from contamination with heavy metals, for studies on plant nutrition led Liebig, Vanselow and Chapman[12] to compare distilled water with demineralized water. They found that objectionable traces of heavy metals in distilled water could be removed by passage through cation exchange resins and that low-cost water of sufficient purity for plant nutritional studies could be obtained from tap water by de-ionization. Hewitt's[13] studies were confirmatory, and he emphasized that the effectiveness of removal of specific ions is inversely proportional to the total concentration of the other ions present.

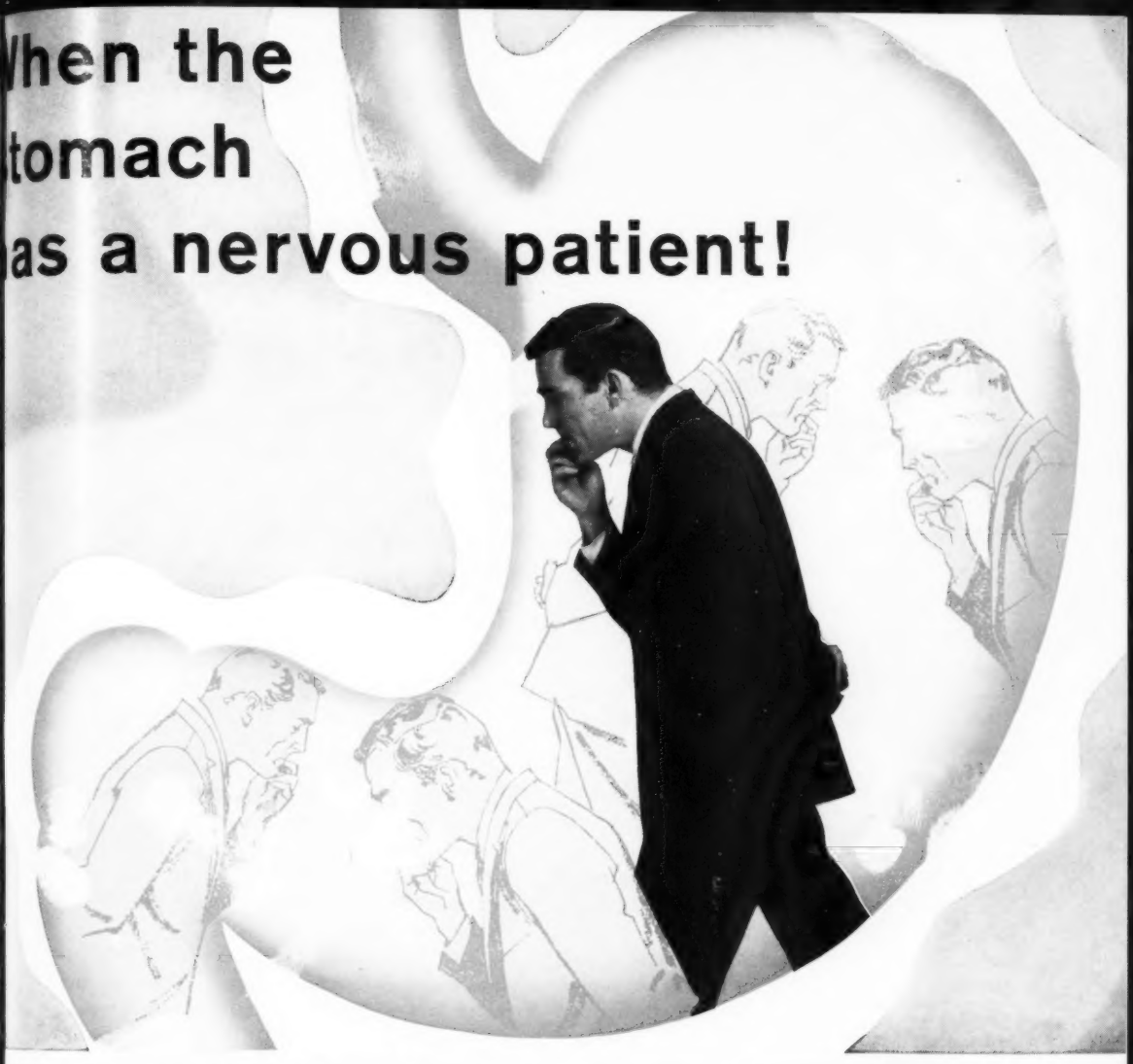
Extremely sensitive test objects are animal cells in tissue culture in synthetic media which lack the buffering capacity of the plasma in natural media. This was emphasized by Healy, Morgan and Parker,[14] who, realizing the crucial importance of the quality of distilled water used in synthetic media, tested the trace metal content of water after various methods of purification and storage. It can be seen from their data in table 1 that water of high purity was obtained by redistillation in PYREX® apparatus or by passage of once-distilled water through a mixed-bed de-ionizer. Subsequent storage conditions clearly could make this water unfit for biologic use, as is seen in the table.

Copper is a common contaminant in distilled water because of the use of copper piping and containers. Copper is undesirable even in minute amounts because of its catalytic properties. For example, it may cause sodium thiosulfate solutions to decompose quite rapidly.[15] Wilson[16] noted that for two months after cleaning a still (with a tin-plated copper condenser and storage tank and a plain copper pipe between the two) the water was highly bactericidal due to the presence of copper in the distilled water.

Repeated poor recoveries of cortisone and cortisol from urine by paper chromatography were traced by Lewbart and Mattox[17] to the presence of 1 ppm of copper in the distilled water which was used to rinse the glassware. Rinsing the glassware with copper-free water from a de-ionizer greatly reduced the losses, which, however, were not completely elimi-

(Continued on page A-26)

When the stomach has a nervous patient!



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antispasmodic/sedative

relaxes the tense patient and his jittery stomach...without the sedative "build-up" many patients experience with phenobarbital preparations.

BUTIBEL combines the "time-matched" components—BUTISOL SODIUM® butabarbital sodium 15 mg. and extract of belladonna 15 mg.—each having approximately 5 hours' duration of effect. Thus, with Butibel there is no overlapping sedation, no antispasmodic gap—t.i.d. dosage keeps the patient comfortable without sluggishness.

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TABLE 2

EFFECTS OF TREATING 250 ML. CHEMICAL GLASSWARE FLASKS WITH 200 ML. OF GENTLY BOILING REAGENTS FOR SIX HOURS*

	TYPES OF GLASSWARE			
	Pyrex	*Vycor®*	*Kimble*	*Glasbake®*
Major constituents of glass (per cent)				
Silicon dioxide	81.0	96.3	74.7	78.4
Boric oxide	13.0	2.9	9.6	14.0
Other oxides (chiefly aluminum oxide)	2.2	0.4	5.6	2.5
Losses in weight (milligrams); average of three successive treatments				
Water	0.2	0.1	0.1	0.3
1 N sulfuric acid	0.4	0.1	0.5	0.8
Hydrochloric acid (constant boiling, approximately 6 N)	2.2	0.4	2.6	4.6
Sodium chloride (5 per cent unbuffered)	2.2	0.5	0.7	12.8
0.05 N sodium hydroxide	90.9	43.3	55.3	94.1
0.5 N sodium hydroxide	287	—	173	251

*Data selected from Wichers, Finn and Clabaugh.[22]

nated until small amounts of ethylenediaminetetraacetic acid (EDTA) were added to the residue in the tubes.

Ellerbrook and Davis[18] found the cause of low photometric oxyhemoglobin determinations to be copper contaminating the distilled water. The 2.4 ppm of copper present presumably came from copper tubing or copper lining of a storage tank. Their investigation led them to conclude that oxyhemoglobin was converted to alkaline methemoglobin by copper in dilute alkaline solution, and that as little as 0.3 ppm of copper would result in a 10 per cent decrease in optical density in measuring oxyhemoglobin at a wavelength of 550 μ.

Storage of Purified Water

An outline of the problems of storing purified water was presented by Saunders and Shotton.[19] Contamination can be of two types, either due to the growth of microorganisms or due to the solvent properties of water which lead to attack on the container material during storage.

Rubber—Contact of water with rubber stoppers or rubber tubing may render it completely unsuitable for purposes such as serving as a solvent for tissue culture media.[20] Contaminants extracted from rubber may absorb ultraviolet light, making water unsuitable for spectrophotometric measurements in this part of the spectrum.

Glass—Dimbleby[21] published an excellent discussion of the properties of glass as they relate to the problem of storage. In general, glasses which are least likely to result in contamination have the greatest chemical resistance, high thermal resistance, and high mechanical strength; they also are more difficult to mold and much more expensive than glasses with higher alkali content. When water is in contact with glass, hydrogen ions replace the alkali in the glass, and, as the water then becomes alkaline, the silica framework of the glass is decomposed. Theoretically, fused silica will resist water and acids (except hydrofluoric acid), but all silica-containing glasses are attacked by alkaline solutions and cannot be used for their storage. Table 2 shows the degree to which different types of glass are attacked, as measured by loss of weight of the

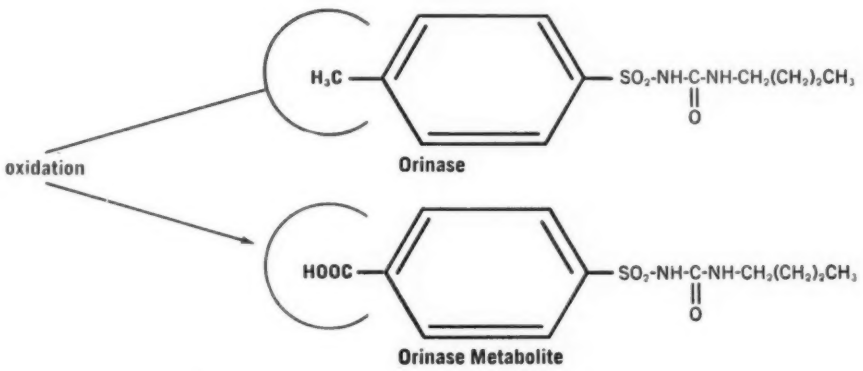
(Continued on page A-28)

Why is the methyl "governor" in Orinase so important?

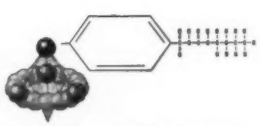
One of the most significant advantages of Orinase therapy is the rarity of associated hypoglycemic reactions.

This widely-reported clinical benefit is a function of the exclusive Orinase methyl "governor." Lending itself to ready oxidation (principally, it is thought, a hepatic process), the methyl group ensures prompt metabolic inactivation of the Orinase molecule. What actually happens is that a rapidly- and continuously-excreted carboxy-metabolite is produced that has no hypoglycemic activity at the existing levels.

As a result of the oxidation of its methyl group, Orinase shows a decline in activity soon after it reaches its effective peak in the plasma. Maintenance dosage serves to reduce blood sugar levels to normal, but rarely below that point, and there is no reported problem of accumulation.



Orinase*



An exclusive methyl "governor" minimizes hypoglycemia

Indications and effects: The clinical indication for Orinase is stable diabetes mellitus. Its use brings about the lowering of blood sugar; glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear.

Dosage: There is no fixed regimen for initiating Orinase therapy. A simple and effective method is as follows: *First day*—6 tablets; *second day*—4 tablets; *third day*—2 tablets. The daily dose is then adjusted—raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

Patients receiving insulin (less than 20 units)—discontinue insulin and institute Orinase; (20 to 40 units)—initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units)—reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed. In candidates for combined Orinase-insulin therapy, an individualized schedule is usually obtainable during a trial course of two or more weeks.

Contraindications and side effects: Orinase is contraindicated in patients having juvenile or growth-onset, unstable or brittle types of diabetes mellitus; history of diabetic coma, fever, severe trauma or gangrene.

Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of translation from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 650,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:
Tolbutamide ..... 0.5 Gm.

Supplied: In bottles of 50.

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June, 1961

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glass containers after various solutions have been boiled in them.[22]

Metal—Metal tanks should always be enclosed; otherwise, appreciable amounts of suspended matter may appear. Although some kinds of stainless steel are suitable, traces of heavy metals are likely to appear after long storage.

Polyethylene—The most suitable lining for plumbing and containers in contact with purified water is polyethylene. After prolonged storage in polyethylene, very little change occurs in good purified water.[14, 19]

Summary

On any reasonable scale of operation, it is almost impossible to obtain water that is free of all impurities. The choice between deionization and distillation depends on many factors, including the composition of the raw water, the specific purity requirements of the individual situation, and economics. Improper handling or storage will destroy the usefulness of even the finest purified water.

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MEETINGS and Postgraduate Courses

First Inter-American Conference on Congenital Defects, Los Angeles: To be held at the Statler Hotel, January 22-24, 1962, under the sponsorship of the National Foundation and the University of Southern California. For further information, write to: Stanley E. Henwood, Executive Secretary, International Medical Congress, Ltd., 120 Broadway, New York 5.

University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore: Postgraduate courses to be held in 1962:

Advances in medical science, January 10-May 16
Endocrinology and metabolism, January 12-13
Clinical anatomy, January 29-May 21
Clinical cardiology, February 1-3
Hematology, March 8-9

For further information, write to: Committee on Postgraduate Education, University of Maryland School of Medicine, Baltimore 1.

University of Texas M. D. Anderson Hospital and Tumor Institute, Houston: Annual symposium on fundamental cancer research, "Conceptual advances in immunology and oncology," March 1-3, 1962. For further information, write to: Publications Department, University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

RENAL SYMPTOMS IN DIABETES

American Diabetes Association, New York:

• A high index of suspicion of diabetes is desirable in the differential diagnosis of any renal involvement of uncertain etiology, especially if there is evidence of neuropathy, retinopathy or the nephrotic syndrome or a family history of diabetes. Renal and vascular lesions may be integral parts rather than complications of diabetes. Three patients with fully developed diabetic nephropathy were seen with normal fasting blood sugar levels and consistent aglycosuria. Glucose tolerance curves demonstrated association of the lesions with diabetes.—Dr. Max Ellenberg, Mount Sinai Hospital, New York.

SODIUM TOLERANCE OF DIGITALIZED CARDIACS

American Therapeutic Society, New York:

• The daily administration of 12 gm. of sodium chloride to patients digitalized for congestive heart failure satisfactorily overcomes the difficulty of insuring that the diuretic is received at similar stages of fluid retention. On the basis of their response to sodium loading, patients fall into four categories. Patients in group 1 accumulate peripheral fluid rapidly and steadily, but the trend can be reversed by potent orally administered diuretics in spite of continued administration of 12 gm. of salt daily. About 75 per cent of the remaining patients fall into the other three groups and will retain 5 lb. or less of fluid without detriment. Results show that universal sodium restriction of digitalized cardiac patients is unjustified, particularly since the advent of potent orally given diuretics. It seems more realistic to ascertain the patient's tolerance to sodium.—Dr. Solomon Fisch, Veterans Administration Hospital, Bronx, New York.

• A new cortical stimulant, vanillic acid diethylamide, injected three times weekly, proved of value in catatonic and involutional depressions. Patients with paranoid tendencies were also stimulated, but their paranoid tendencies were increased. It appears the drug will approach the effectiveness of electroshock and will be safer.—Dr. M. J. Miller, Hahnemann Medical College and Hospital, Philadelphia.

• In the majority of seven patients with diabetes insipidus, satisfactory control of polydipsia and polyuria has been obtained with the oral administration of chlorothiazide or related compounds and spironolactone. Mode of action may be based on alteration of electrolyte metabolism associated primarily with natruresis.—Dr. Herbert S. Kupperman, New York University School of Medicine, New York.

HOST RESISTANCE IN CANCER

American College of Chest Physicians, New York:

• Data indicating a humoral cytotoxic antibody can be elicited by an injection of autologous tumor homogenized in Freund's adjuvant. Volunteer patients with terminal cancer received intramuscular injections of their tumor antigen. An inflammatory reaction characterized by erythema, swelling, edema, heat and tenderness at the tumor site was noted 15 to 25 days later. In vivo cytotoxicity studies were conducted with Cohn fractions I, II and III. Sixty-three per cent of the injected subcutaneous nodules became nonpalpable within 10 days. Five per cent grew and became measurable again. Reintroduction of the same antibody protein caused the nodules to become nonpalpable. These same Cohn fractions had no effect on the patient's normal tissue.—Dr. Russell H. Wilson, Veterans Administration Hospital, Houston.

• It is seldom emphasized that many men undergo a severe emotional upset during middle age. This reaction is characterized by insecurity, depression, anxiety, tension states, hypochondriasis, alcoholism and psychic impotence. Cardiovascular and cardiopulmonary conditions may worsen this reaction, or this emotional disturbance may prevent the successful rehabilitation of the individual.—Dr. John F. Briggs, University of Minnesota Medical School, Minneapolis.

EPISTAXIS LINKED WITH ALLERGY

National Medical Association, Inc., New York:

• Recurrent or periodic nosebleeds may be associated with an underlying and possibly unrecognized allergic state. In a group of 450 children, the incidence of recurrent epistaxis was 8 per cent larger among those with allergic manifestations, particularly allergic states involving the upper respiratory tract. Local cauterization will not give lasting benefit unless the allergy is treated.—Dr. Roselyn P. Epps, Howard University College of Medicine, Washington, D.C.

INFECTIONS IN THE NEWBORN

West Virginia State Medical Association, White Sulphur Springs, W. Va.:

• It may be that physicians have been lulled into a false sense of security by the relatively greater effectiveness of control measures for infectious diseases in older infants and children, and, just as important, that they often fail to recognize that the death of a newborn infant has been due to infection rather than prematurity and atelectasis. Infections in the newborn period continue to be a health problem because of transmission of infection through the birth canal, the relative resistance of the more common pathogens of the newborn to antimicrobials, the increased susceptibility and low resistance to infection in this age period, and the atypical clinical patterns of infection.—Dr. Waldo E. Nelson, Philadelphia.

• For every person with true myxedema, there are a thousand or more who are receiving thyroid because of "lack of pep," "glandular obesity," and other conditions in which thyroid does not seem to be indicated. Use of estrogens is important for many women seriously disabled by menopausal symptoms, but the majority of women are able to live without hormonal therapy.—Dr. Edward H. Rynearson, Mayo Clinic, Rochester, Minn.

• Control of diabetes mellitus should be as good as is consistent with the avoidance of hypoglycemia. Recently, good standards of control regrettably have been relaxed in many patients taking the orally administered agents. Convenience of therapy has been permitted to override principle.—Dr. Henry T. Ricketts, University of Chicago School of Medicine, Chicago.

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(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., et al.: Diabetes 7:398, 1958.

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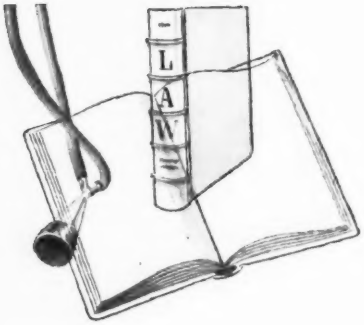

Forensic Medicine

OLIVER C. SCHROEDER, JR.*

Drug Automatism as a Cause of Pseudo Suicide

BENGT JANSSON†

University of Göteborg, Göteborg, Sweden

Editorial Comment

In the October 1960 issue of this Journal, an article was published entitled "Barbiturates, automatism and suicide," by Mr. Rowland H. Long. The following discussion by Dr. Bengt Jansson, Göteborg, Sweden, was written in response to Mr. Long's presentation. Since forensic medicine cases often stimulate conflicting opinions, the Editor deems it appropriate to publish Dr. Jansson's comments, which reveal his experience with the fascinating problem of drug automatism.

The views expressed in Mr. Long's and Dr. Jansson's articles do not necessarily reflect the opinion of the editor of this department.—Oliver C. Schroeder, Jr.

MR. Rowland Long, who doubts the occurrence of automatism, has stated that there are no authenticated cases of this phenomenon to be found in the literature other than the three reported by Richards in 1934.[1] Ettlinger and Flordh,[2] however, gave an account in 1955 of a study consisting of 500 consecutive cases of attempted suicide seen at Södersjukhuset in Stockholm, Sweden, during 1952 and 1953. These authors mentioned "serial consumption" as a contributory factor in not less than 27.8 per cent of the cases of poisoning. There was no difference in incidence between men and women.

BENGT JANSSON

Lindberg[3] has long believed that serial consumption, or automatism, is a mechanism frequently present in many so-called attempted suicides. He has recommended that when hypnotics are being prescribed patients should be instructed never to have more than one or

(Continued on page A-36)

*Director, The Law-Medicine Center, and Professor, School of Law, Western Reserve University, Cleveland, Ohio.

†Psychiatric Clinic, Sahlgrens Hospital, University of Göteborg, Göteborg, Sweden.

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1. Hock, C. W.: Am. J. Gastroenterol. **34**:293 (Sept.) 1960.

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TABLE 1

DISTRIBUTION OF ATTEMPTED SUICIDES ACCORDING TO VARIOUS TYPES

TYPE	MEN		WOMEN		TOTAL	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
Type S	68	31.8	81	29.6	149	30.5
Type I	70	32.7	119	43.4	189	38.7
Type A (automatism)	64	29.9	60	21.9	124	25.4
Doubtful or combination of different types	10	4.7	12	4.4	22	4.6
Probable accidents	2	0.9	2	0.7	4	0.8
TOTAL	214	100.0	274	100.0	488	100.0

two tablets at hand, in order to avoid a "tablet accident." The aim of my investigation was to attempt to find some expression for the incidence of automatism from a study of attempted suicides. A detailed description of the conduct and result of this investigation has been given elsewhere.[4]

The present study concerns the attempted suicides examined at the Psychiatric Clinic, Sahlgrens Hospital, University of Göteborg, Göteborg, Sweden, during 1960. It consists chiefly of all the attempted suicides in Göteborg (a city of 400,000 inhabitants). Of these, 488 patients (214 men and 274 women) required hospitalization or psychiatric outpatient care. In regard to age distribution, seasonal variation, manifestations of previous psychic illness, etc., this study agrees largely with previous Swedish investigations, particularly that of Ettlinger and Flordh. Certain features of this investigation could be interpreted as showing that attempted suicide has less relation to psychic insufficiency in women than in men.

The attempted suicides have been divided according to their different character, as follows:

1. Serious attempts, in which the patient has harbored suicidal wishes for some time. The desire to commit suicide perhaps lingers on even after the actual attempt has been made. The patient's psychic condition in any case makes it appear that there is a distinct risk of renewed attempts at suicide (table 1, type S).

2. Impulselike attempts, in which the act is committed without premeditation in connection with some transitory effect (table 1, type I).

3. Attempts where, on the whole, there has been no intention to commit suicide, even temporarily in connection with some effect or other. All these are cases of poisoning. I regard the mechanism in such cases as automatism. The person involved has perhaps been in a state of psychic stress for some time. He first takes a tablet "to get some sleep," but in his tense and overwrought state it does not have the desired effect. He is much too restless to wait for the tablet to take effect. He then takes two more tablets, and gradually enters a semiconfusional state. He is no longer able to act purposively and, if the bottle of tablets is within reach, he may go so far as to empty it (table 1, type A). The following is an example of this type of attempted suicide.

In connection with her mother's death in 1956, a 24 year old woman had a period of depression. For a period beginning at the end of March 1960, she had a certain agitation and pain in the diaphragm. She also was worried over the search for new employment. On May 6, 1960, she first took a few tablets in order to get a good, long sleep. (Her foster mother was in an adjacent room.) The young woman never intended to take her life, and she had never felt sick of life. As she did not fall asleep as quickly as she wanted, she took more and more tablets, one after another, until

(Continued on page A-38)

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she had taken a total of 20 gm. meprobamate. She had no recollection of having taken so much. She was admitted to the hospital in a state of coma and had to be kept in a respirator for three days. She was then transferred to the psychiatric clinic, but was completely free of depression, even on her admission there on May 14. She was discharged after only one week, on May 21, her state of illness being characterized as a reactive insufficiency.

The distribution of attempted suicides according to the three types described is given in table 1. Not less than 25.4 per cent of the cases in this study were considered to be of type A.

A study of the type A cases in relation to the psychiatric diagnoses showed a clear overrepresentation among the cases of automatism of diagnoses in which there had been a reason to suspect a high incidence of cerebral organic conditions. This applied particularly to diagnoses such as alcoholism, narcomania, epilepsy and senile dementia. Not less than 49.2 per cent of the cases of automatism fell within one of the diagnosis groups, compared with only 24.5 per cent of the rest of the material. However, in regard to the degree of severity of the somatic effects, there is no difference between a case of automatism and an attempted suicide. A study of the seasonal distribution of the cases of attempted suicide presented further evidence that automatism is a clinical unit.

The objection may be raised that it must be very difficult to assert with any confidence that a particular attempt at suicide is of the automatism type. That is true. If, like Mr. Long, we consider the legal aspect, it must be regarded as impossible to attain complete certainty. Support for a clinical interpretation, however, is often forthcoming from the objective information that the patient's relatives can supply. They may be able to confirm that the patient took his tablets one after another. They even can state that when the patient took the tablets he did not avoid the company of other people or disclose any ideas of suicide. In Sweden, the kind of evasion which may be current in the United States is lacking, as attempted suicide is not followed by any legal consequences in the former country. On the contrary, the opinion is often held that an attempt to commit suicide is to be regarded as a cry of distress with a call for help and care when the patient has absolutely no interest in dissimulation regarding his suicidal intentions.[5]

It also must be pointed out that automatism is a mechanism which is completely understandable from the psychopathologic point of view. I cannot agree with Mr. Long's opinion that it is unreasonable to assume its occurrence, since the only result of a serial consumption would be to put the victim to sleep before he had succeeded in taking enough tablets to produce a stage of fatal intoxication.

In such cases, it is a question of patients who often are in a state of serious anguish. It is a common psychiatric experience that it may be exceedingly difficult to get such patients off to sleep, whatever means are employed. In many instances, these persons have acquired a considerable resistance to drugs during previous periods of alcoholism or narcomania. In addition, an alcoholic often has sustained cerebral damage and may thus have a tendency toward a pathologic reaction to drugs, thereby slipping into a confusional state more easily. Certainly, a healthy person under the influence of barbiturates and other sedatives may reach a confused state in which he does not notice that he is taking the remaining tablets. This is perhaps even more likely where ataraxics are concerned. The paradoxical irritation which sometimes arises under the influence of narcotics is also well known. In my study, ataraxics accounted for 20.9 per cent of the poisoning cases, barbiturates 46.9 per cent, barbiturates in combination with ataraxics 9.8 per cent, and other or unknown drugs 22.4 per cent.

All deaths in which it can be shown that the victim had consumed a large dose of hypnotics and was found with an empty sleeping tablet bottle beside the bed are reported as suicides. Many of these undoubtedly would be better characterized as accident cases.

I intend to follow up this investigation with a catamnestic study in order to ascertain how

(Continued on page A-40)

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*Bibliography available on request.

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many persons have actually committed suicide after a certain period of observation. By this means, it may be possible to judge how much importance, from the viewpoint of prognosis, is to be attached to a pseudo attempt at suicide that has been classified as automatism.

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*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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Radiology

PAUL C. HODGES*

Gout

THE term "gout" did not appear in the English language until late in the thirteenth century, but skeletal manifestations of this ancient disease have been found in Egyptian mummies and in prehistoric European man. Hippocrates (460 to 377 B.C.) wrote of it; Paracelsus (1493 to 1541) recognized it as "a tartaric process caused by precipitation of substances ordinarily voided from the body," and Sydenham (1624 to 1689), writing in Latin in 1675, produced a treatise on gout which is considered his masterpiece and in English translation continues to be read almost 300 years later.

The centuries-old belief that gout is caused by overindulgence in coitus, wine and rich food led to innumerable anecdotes and cartoons;[1] however, although internists today impose dietary restrictions on patients with severe tophaceous gout, they no longer believe the disease is caused by dietary or sexual indiscretion.

Alexander of Tralles (525 to 605 A.D.) used the corm (bulb) of meadow saffron (*Colchicum*) in treating arthritic patients, some of whom presumably had gout. For nearly 150 years its alkaloid, colchicine, has remained a therapeutic cornerstone, augmented within the decade by the uricosuric agent probenecid, a benzoic acid derivative employed originally to enhance the action of penicillin by reducing its excretion in the urine.

With the years since Paracelsus' shrewd observation, evidence has accumulated confirming the fact that gout is caused by some aberration in the metabolism of uric acid, but the details of its metabolism are so intricate that little progress was made in understanding the underlying physiology until Garrod's qualitative "string" test for uric acid in the circulating blood had given way to precise quantitative methods. Now, with the aid of isotope tagging, certain biochemical findings, formerly seemingly inconsistent, are beginning to make sense. The older medical dictionaries do not contain some of the biochemical terms now in common use by "goutologists," and only in the most recent monographs[2-4] and papers[5,6] will one find reasonable answers to much that formerly was only dimly understood.

Uric Acid Metabolism

The body of the normal human subject contains approximately 1500 mg. of uric acid, of which one-sixth circulates in the blood,

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maintaining plasma levels of about 5 mg. per 100 ml. in adult males and about 4 mg. per 100 ml. in children and premenopausal women. This uric acid arises from three sources and is eliminated by two means. Unlike most other mammals, man does not produce in his body the catalyst uricase to enable him to degrade uric acid into simpler constituents.

The three sources of plasma uric acid are (1) ingested nucleoproteins, (2) breakdown of body tissues, and (3) synthesis from glycine and other substances of inosinic acid, which may be incorporated into body tissues and eventually broken down into uric acid or, by a short-circuit process, synthesized directly into uric acid in a manner analogous to that which is the rule in birds and some reptiles.

Two-thirds of the uric acid in the body is eliminated by glomerular filtration, with subsequent active reabsorption and active secretion by the renal tubules; one-third is delivered into the gastrointestinal tract (in saliva, bile and pancreatic juice), where the uricase of intestinal bacteria accomplishes uricolysis.

The exact relation between hyperuricemia and acute attacks of gouty arthritis remains unknown. Some hyperuricemia is symptomless, while some acute gout occurs at times when plasma uric acid concentrations are normal.

Primary Gout

Primary gout is a hereditary disease, predominantly of adult males, in which the plasma uric acid may rise to double or even triple normal levels, usually because of increased production but occasionally because of decreased renal elimination. The exact role of heredity is not clear, but it may act by increasing the amount of uric acid synthesized directly from inosinic acid, a sort of throwback to man's avian and reptilian ancestors.

Secondary Gout

Secondary gout occurs in several diseases in which there is rapid and extensive breakdown of body tissues, either spontaneously or as a result of therapy (for example, polycythemia, resolving pneumonia and some neoplasms). Infrequently, it is caused by diminished uric acid excretion resulting from acquired kidney disease.

Therapy

Colchicine has no effect on the production or elimination of uric acid and exerts no analgesic action on nongouty arthritis; yet, it is highly effective in controlling the seizures of acute gout. Probenecid, which drops serum uric acid concentration by promoting uricosuria, does nothing to relieve the symptoms of acute gout. Together, these two drugs constitute an effective prophylactic team; however, one must be careful not to prescribe salicylates along with them, because the latter negate the action of probenecid.

Tophi

It is the aim of modern physicians to diagnose and control gout before tophi form. If the time comes when this worthy objective is achieved, the radiologist no longer will be concerned in the diagnosis of this disease. Meanwhile, the tophaceous form of gout is all too common, and, when tophi lie in bone (medullary tophi), roentgenography is the best means of detecting them. Tophi are compact, gritty collections of sodium urate crystals lying in bursae, tendons, cartilage or bone; they range in size from a few millimeters to several centimeters and in weight from a few milligrams to many grams. Sodium urate has approximately the same transparency to x-rays as do the soft tissues; thus, it is only in bone that tophi stand out sharply contrasted from surrounding tissue as "negative shadows." Secondary calcification in a tophus is a late and unusual phenomenon.

The mechanism of tophus formation is not understood. Perhaps some local tissue factor initiates deposition of crystals in subjects who have hyperuricemia. It is established that physical exchange occurs between the surface layers of existing tophi and the circulating plasma, and that long-continued lowering of uric acid plasma levels leads to shrinking and eventual disappearance of tophi.[7]

Tophi are most common in the toes, fingers, ankles and knees, but they may occur almost

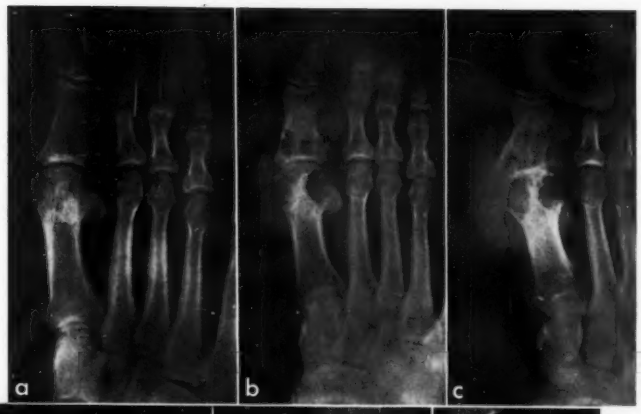

FIGURE 1. a. Typical medullary tophi in a typical location, observed in a 42 year old patient with severe, progressive podagra who was seen 18 years after onset of symptoms.

b. Appearance of tophi four years later.

c. Appearance of tophi seven years after first x-ray was made and six years before the patient died of massive coronary thrombosis. Tophaceous material obtained at tophectomy showed (by polarized light) characteristic bundles of crystals of sodium urate.

2.

3.

FIGURE 2. Medullary tophi in radius, carpal bones, heads of second, third and fifth metacarpals, and several phalanges, seen in a 61 year old man with symptoms of 13 years' duration. In this case, gout was mistaken for rheumatoid arthritis. Typical lesions also were present in the right great toe and other foot bones.

FIGURE 3. a. Medullary tophi in head of the humerus in a 63 year old man known to have gout.

b and c. Tophi in the left first metatarsophalangeal joint (b) and in the right foot (c) are more typical.

This case would have been difficult to diagnose from the appearance of the tophi in the head of the humerus alone. The tophaceous nature of the lesions was confirmed subsequently by biopsy at several sites.

anywhere, including the bridge of the nose.[7]

X-ray Diagnosis

In most cases seen by radiologists, the referring physician and his patient know only too well that the latter has gout (figure 1), but, occasionally, the roentgenographic finding of small medullary tophi in the fingers or toes of a patient thought to have rheumatoid arthritis or osteoarthritis may be the first clue to the true diagnosis (figure 2). It is in such cases that the radiologist is most useful. The well-equipped blood chemistry laboratories connected with vigorous metabolism services in major institutions frequently are able to detect genuine hyperuricemia in patients previously thought to have normal uric acid levels. Not all small, "punched-out" osteolytic lesions in the fingers and toes are medullary tophi, but the likelihood of gout is great enough to

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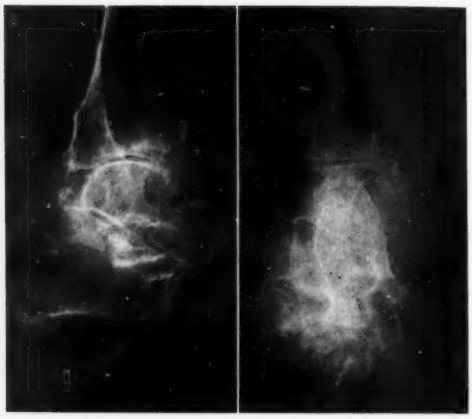

5.

FIGURE 4. Small medullary tophi in a 39 year old man who had had gout for 19 years. Small tophi were observed in the cartilage of the ears, and large ones were seen in the soft tissue of the hands, elbows, knees and toes.

The soft-tissue tophus at the second metacarpophalangeal joint is clearly seen, but at this time medullary tophi were minimal. Large, typical medullary tophi later developed in the toes, fingers, elbow and elsewhere.

FIGURE 5. Two views of extremely severe gout of left ankle simulating infection or neoplasm, seen in a 57 year old man who had had gout for 18 years. Typical medullary tophi were seen in the patient's hands and feet.

Subsequent to this examination, the patient had 68 gm. of tophaceous material removed from his left ankle. Had it not been known that he had gout, the extensive destruction of metatarsals, tarsals and the lower end of the fibula might have been considered due to a synovial neoplasm or sepsis.

warrant submitting patients with such lesions to the most painstaking search for hyperuricemia. Such a search requires not only unusually well-equipped and well-staffed blood chemistry laboratories but also careful control of the patient for some days preceding withdrawal of the blood for the test. Excessive ingestion of foods rich in nucleoproteins might give a fictitiously high plasma uric acid level, and, almost certainly, medication with salicylates or other uricosuric agents could mask a significantly high hyperuricemia.

Small tophi in large bones such as the head of the humerus (figure 3a) may need the support of the history or of more characteristic lesions elsewhere in the skeleton (figure 3b and c); sometimes, soft-tissue tophi, easy to see by direct inspection or in x-ray films, may be accompanied by only a few small medullary tophi (figure 4).

When gout is extremely severe (figure 5), the replacement of bone by tophaceous material may be so extensive that the roentgenogram of a large joint, such as the ankle, unsupported by history, blood chemistry or roentgenograms of more typical lesions in hands or feet, may suggest an incorrect diagnosis of osteomyelitis or neoplasm.

Comment

In spite of all that has been learned about gout over the centuries, particularly in the past decade, innumerable questions remain unanswered. Workers in this field may well philosophically say of gout what Kennan[8] recently said of United States-Soviet relations (quoting out of context from Bismarck): "Let us leave a few problems for our children to solve; otherwise they might be too bored."

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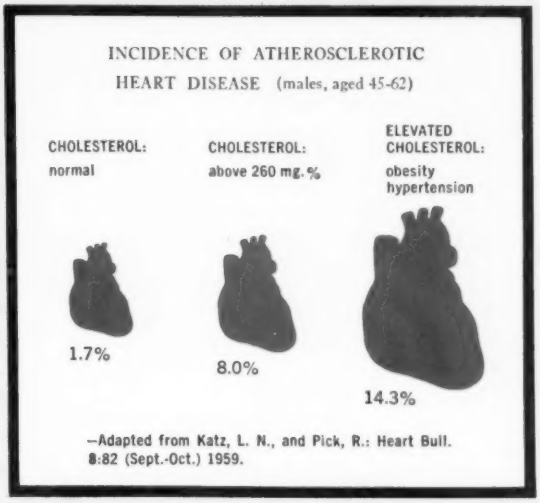
. . . what we are learning about atherosclerosis

WHY MER/29 MAY FAVORABLY ALTER ATHEROSCLEROSIS

It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."
Page, I. H.: Mod. Med. 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease. On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."
Stamler, J.: Am. J. Pub. Health 50:(Pt. 2) 14 (Mar.) 1960.


INCIDENCE OF ATHEROSCLEROTIC HEART DISEASE (males, aged 45-62)
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CHOLESTEROL: above 260 mg.%
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14.3%
—Adapted from Katz, L. N., and Pick, R.: Heart Bull. 8:82 (Sept.-Oct.) 1959.

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AUSTRALIA

The nephrotic syndrome—Results of a 10 year study of 117 cases of nephrosis have been reported in the *Medical Journal of Australia* by Dr. J.H. Coldbeck, Royal Children's Hospital, Melbourne. Approximately 12 new cases (usually in young children) were diagnosed every year. In the majority of those patients in whom the nephrotic syndrome appeared in childhood, the disease was caused by membranous nephritis. A major complication was severe infection, especially chest infection, peritonitis and gastroenteritis. There were 27 deaths in this series, a mortality of 23 per cent.

Treatment included a high-protein diet with restricted salt intake, fluid restriction, administration of diuretics, and specific treatment for infections and other complications. After an initial period of observation, steroid therapy was started. The most satisfactory dosage schedule was found to be that of Drs. Riley and Scaglione, Babies Hospital, New York. Under this schedule, the patient who is less than three years old is given 40 mg. prednisone or prednisolone per day in divided doses. Medication is continued until there is clinical improvement and the sedimentation rate is normal, usually requiring a period of two to three weeks. The dosage is then reduced over a period of three to five days. If the illness does not recur and there is no albuminuria during the following three months, the daily dosage is given for three or four days every two weeks. If the disease has not recurred at the end of six months, steroid therapy is discontinued. If the case is refractory, other measures may be necessary.

BRAZIL

Stenosing rectitis—In *Revista paulista de medicina*, O. Simonsen and co-workers have presented the results of a study of 46 cases of stenosing rectitis of lymphogranulomatous origin. In this series, 15 patients were given sulfadiazine or SULFATHALIDINE® as initial clinical treatment, and the remaining patients received

(Continued on page A-84)

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chlortetracycline or oxytetracycline (1 gm. per day for 20 days). All patients required surgery to correct residual lesions which did not respond to clinical treatment.

The patients who were treated with broad-spectrum antibiotics had good results; those treated with sulfonamide drugs showed a high incidence of recurrence and complications. The authors advocate using broad-spectrum antibiotics to treat anorectal inflammatory processes of lymphogranulomatous origin, as the use of these drugs has improved the prognosis considerably.

Leishmaniasis americana—T. A. Furtado has reported in *O Hospital* on 10 patients with leishmaniasis americana who were treated with amphotericin B. Five of these patients had been treated previously with antimonial or arsenical drugs, or both, with no improvement; the other five had not received any treatment.

Tablets of amphotericin B were administered to five patients in total dosages ranging from 36 to 240 gm., with poor results or no effect. Subsequently, all 10 patients received intravenously a maximal daily dose of 50 mg. of amphotericin suspended in 500 ml. of an aqueous 5 per cent dextrose solution, given over a period of three to four hours. Total dosages ranged from 200 to 1,450 mg. No relapse was noted during follow-up periods ranging from 15 days to 10 months.

Excellent results, with complete healing of cutaneous and mucous lesions, were obtained in all patients. Clinical observation and controlled laboratory studies, including liver function tests, urinalyses, blood counts and electrocardiograms, demonstrated good tolerance to the drug and no toxicity. The only side effects were febrile reactions and slight venous irritation. The author concluded that amphotericin B is effective in treating leishmaniasis americana.

ENGLAND

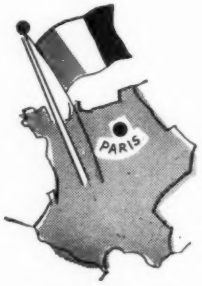
New broad-spectrum penicillin compound—Two years ago there was reported in this column the discovery by research workers in the Beecham Research Laboratories, Brentford, of a process for manufacturing the penicillin "nucleus," which made possible the preparation of new penicillin compounds without the defects of penicillin G. The latest of these compounds has been announced in a series of articles in the *British Medical Journal*. It is of special interest because it is acid-stable (and thus can be given orally) and active against a wide range of gram-positive and gram-negative bacteria. It has been named Penbritin, and the compound (B.R.L. 1341) is 6[D(−)α-aminophenylacetamido] penicillanic acid.

The activity of this compound against gram-negative bacilli is similar to that of tetracycline and chloramphenicol. Against species of *Salmonella* and *Hemophilus influenzae*, Penbritin is slightly more active than penicillin G, tetracycline or chloramphenicol; it is more active than tetracycline and only slightly less active than penicillin G against pyogenic cocci. The compound is not stable to penicillinase and therefore not active against penicillin-resistant staphylococci or other penicillinase-producing organisms.

Penbritin is well absorbed orally, and some 30 per cent of a given dose is excreted in the urine within six to eight hours following administration. The dosage suggested at present is 250 mg. every six hours for treatment of infections due to gram-positive organisms or to *H. influenzae*. A dosage of 250 to 500 mg. every six or eight hours is suggested for infections of the urinary tract, in view of the high concentration of Penbritin obtained in the urine.

It appears from these preliminary reports that the previous broad-spectrum antibiotics may be superseded. In addition, the ease of administration and the wide range of activity of Penbritin are likely to make it widely acceptable to physicians and their patients.

FRANCE



Treatment of pancreatitis—Dr. de Ferron, Nantes, has reported in *La Presse médicale* on the dangers and advantages of draining the pancreatic duct at the start of large-scale paroxysmal attacks of acute pancreatic hemorrhage. Surgery is usually performed during the first few hours of such attacks in the belief that an ulcer has perforated. This opinion is based on the inconclusive evi-

(Continued on page A-86)

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dence of roentgenograms and the results of laboratory examinations which show amylase in the blood. Dr. de Ferron stated that although drainage of the pancreatic duct is sometimes very difficult, it results in an immediate cure. This procedure stops the pain and the steatonecrosis of the cells. Surgery also generally uncovers a stenosis at the end of the canal, the dilatation of which will protect against recurrence. Dr. de Ferron therefore advocates systematic surgical drainage during the first few hours of acute hemorrhagic pancreatitis.

A conference held in Paris reflected various opinions concerning the treatment of pancreatitis. Professor Hepp, Paris, emphasized the great frequency of authentic cases of acute hemorrhagic pancreatitis with regional and lymph node necrosis, but without dramatic intensification of symptoms. In such cases, the diagnosis is based on indirect signs, roentgenograms, the absence of pneumoperitoneum and of obstruction of the small intestine, segmental dilatation of a "sentinel" loop of the jejunum, presence of biliary calculi, and moderate effusion in the left pleural angle. Increased amylase content in the blood is a major sign, although it is not always present.

The prognosis is not good when pancreatitis coexists with nephritis, increased leukocytic count, low blood sugar level, low thrombin content in the blood, and a calcium level below 80 mg., which indicates that large plaques of cytosteatonecrosis are binding the calcium. Professor Hepp advocates the use of a pleural puncture to demonstrate "amylothorax" with pancreatic ferments. Abdominal tapping at the pancreatic region will demonstrate a hemorrhagic effusion, but this method is rarely used in France. An electrocardiogram is indispensable, since certain types of posteroinferior infarctions imitate the painful abdominal crisis of pancreatitis.

Although Professor Hepp is a surgeon, he is extremely cautious in the use of surgical intervention. He does not advocate drainage of the pancreatic duct because of the operative shock which accompanies it. He prefers to explore the gallbladder very cautiously, without any manipulation that would drive the bile back toward the pancreas. He also prefers to do a biliary drainage by cholecystostomy, if necessary, and to infiltrate procaine into the pancreatic region. If blood cysts are detected by exploratory laparotomy, they must be opened and emptied. Later, the left splanchna are infiltrated with procaine. Professor Hepp performs peripancreatic infiltration by Waren's method (a POLYTHENE® tube fixed at a permanent site); procaine infiltration is accompanied by intravenous injections of corticosteroids, an essential part of the treatment. An indwelling stomach tube, antibiotic therapy and, if necessary, resuscitation are used. Although antitrypsin therapy is still in the experimental stage, its value as an adjunct to the previously mentioned measures was pointed out.

Professor Caroli stated that when new pancreatic attacks are developing, he performs systematic pancreatic drainage by either a sphincterotomy restricted to the sphincter of Oddi or a biliary intestinal anastomosis into an excluded jejunal loop.

JAPAN

Hard tick infestation in man—In the *Kyushu Journal of Medical Science*, Dr. Kenjiro Kawashima and associates, Kyushu University Medical Faculty, Fukuoka, have reported the first case in Japan of infestation by the hard tick *Amblyomma testudinarium*.

A 58 year old farmer was admitted to the clinic complaining of a foreign body and itching in the anal region. Initially the size of a green pea, the foreign body gradually increased until it became a round polyp 15 mm. in diameter. A hard tick, considerably engorged, was found in the polyp.

The *A. testudinarium* is prevalent in India, Ceylon, Burma, Indochina, Borneo, Malaya, the Philippine Islands, Indonesia, Formosa and Japan. The adult tick infests a wide variety of both wild and domestic animals. Currently, the only tick-borne diseases in Japan on which there are data are tularemia and piroplasmosis.

Prevention of reflux esophagitis—Dr. Zen Ishikawa and co-workers, Kobe Medical College, Kobe, have used Bauhin's valve to prevent reflux esophagitis after removal of the gastroesophageal sphincter. Their results have been published in the *Kobe Journal of Medical Science*.

Experiments first were performed to determine whether Bauhin's valve could function like the cardia of the stomach and whether ileocolic graft-

(Continued on page A-88)

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ing was anatomically possible. Several methods of ileocolic grafting were tried on dogs, and it was concluded that the transplanted Bauhin valve was useful in preventing regurgitation. According to the data obtained by esophagoscopy, macroscopy and microscopy, reflux esophagitis did not develop in any of the dogs in this series. In the dogs which survived one year or more, x-ray examination showed that the time required for passage of substances through an adaptation of Bauhin's valve became increasingly shorter. Although the maximal pressure which the valve exerted to prevent reflux differed with each dog, the valve was found to be capable of preventing reflux just as efficiently as does the cardiac sphincter in normal conditions.

Ileocolic grafting then was performed on four selected patients who had successfully undergone total gastrectomy. Reflux esophagitis or subjective symptoms referable to complications did not develop in any of these patients. Although one patient died of carcinomatous peritonitis nine months after operation, necropsy findings showed no evidence of esophageal dysfunction. Initially, these patients complained of epigastric heaviness in the region of the grafted valve after eating; however, this was not noticed after the fourteenth postoperative day. The time required for passage of substances through the transplanted valve became increasingly shorter, and the valve gradually and efficiently replaced the function of the cardia of the stomach, as was demonstrated by repeated x-ray examinations.

SPAIN

Surgical treatment of Parkinson's disease—For the past year and a half, a team of Spanish neurosurgeons has been working with Professor Martin Lagos, Chief Surgeon, San Carlos Hospital, developing surgical procedures used in treating Parkinson's disease. Under the direction of Drs. Gonzalo Bravo, Carlos E. Parera, Maximo Pozas, Portera and Anastasio, this team is doing work considered so important that plans have been made to build an institute for the treatment of diseases of the nervous system, with a special section for parkinsonism.

At present, an estimated 25,000 persons in Spain have Parkinson's disease. Although the causative factors are sometimes unknown, the disease often results from an inflammatory process of the brain (encephalitis). The grippe epidemic in Spain in 1918 also caused a large number of cases.

Surgical treatment consists of two delicate brain operations which eliminate the tremor, rigidity and slowness of movement seen in Parkinson's disease. The operations are based on the work of Dr. Irving S. Cooper, New York. Drs. Bravo and Parera, Madrid, and Dr. Isamat, Barcelona, worked with Dr. Cooper in New York and are now applying his technics to their work in Spain. Since July 1959, 350 operations have been performed in the San Carlos Hospital, with satisfactory results in 80 per cent. Many patients who had been completely incapacitated have now resumed useful lives.

Another new treatment for Parkinson's disease, initiated by Dr. Leksell, Sweden, involves the use of the electronic bistoury. This treatment requires an atomic reactor in which the patient can be placed. Experiments with this technic on animals appear to indicate that the size of the brain lesions produced in parkinsonism can be controlled.

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Local Steroid Injection Therapy in Rheumatic Diseases

NORMAN O. ROTHERMICH*

Ohio State University College of Medicine, Columbus

Local intraarticular and extraarticular administration of steroids is firmly established as a highly effective, dependable method of therapy in rheumatoid arthritis, osteoarthritis and fibrositis. All practitioners who care for patients with these diseases should use the method more frequently. Strict aseptic precautions are necessary relative to the syringe, needle and material injected, and, probably even more important, accurate diagnosis is imperative. More than 75 per cent of the injections produce clinically significant benefit.

NORMAN O. ROTHERMICH

Soon after the clinical application of cortisone by Hench and coworkers, it became apparent that systemic corticosteroid therapy, even in a moderate or low dosage, would produce a generally beneficial effect in rheumatoid arthritis. Often, however, the effect would be only partial or completely absent in one or more joints. It was natural to look for a method of bringing higher concentrations of steroid to the unremitting inflammatory joints without increasing the systemic effect of the steroid. The initial attempt consisted of instilling cortisone directly into the joint. This proved largely ineffective. Despite this failure, Hollander of Philadelphia persisted in attempts to enhance the intraarticular effect of steroids. As soon as hydrocortisone became available, he used it and obtained strikingly beneficial results. In the past decade, many reports dealing with intraarticular steroid therapy have appeared in the literature, but Hollander, in reporting a very great number of such injections, was largely responsible for providing the statistical validity and reliability necessary to make this procedure clinically applicable.

Intraarticular steroid therapy is no longer new; it is well established and accepted by rheumatologists everywhere. It is probably the most decisively effective single therapeutic modality that one can employ for the rheu-

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matoid arthritic patient; it can give the osteoarthritic patient gratifying relief for long periods; it can wipe out severe and seemingly intractable pain and the disability of fibrositis in a matter of hours. It is considered safe, effective and simple, and is an office procedure that requires only a few minutes of time, usually is painless, and should be comparatively inexpensive. At the Columbus Medical Center, this method of therapy has been used for more than eight years for private patients with rheumatoid arthritis and osteoarthritis, and it has been extended to an even more important and more highly effective area of application, namely, in fibrositis. The principal problem now in regard to local steroid injection therapy in rheumatic diseases is to encourage its more widespread use by practicing physicians everywhere.

One of the principal functions of the corticosteroids is to block or inhibit the development of the usual inflammatory reactions to noxious substances. If this inflammation is necessary or purposeful, as, for example, to contain multiplying bacteria and prevent their dissemination to other parts of the body, then obviously the blockage of this inflammatory process by corticosteroids could be harmful and dangerous. However, in most rheumatic diseases the inflammatory process which occurs is not purposeful and is, in itself, disease-producing. Here, the antiinflammatory action of corticosteroids is highly desirable and can be curative or at least disease-arresting. The corticosteroid hormone has multifaceted action in the body, and the physician, in trying to obtain greater antiinflammatory action by increasing dosage, may and often does find that numerous other effects appear that are undesirable and may be harmful or even lethal. It is remarkable that the vast majority of these undesirable effects have been reported almost exclusively among patients with rheumatoid arthritis. I believe these effects have resulted almost entirely from excessive dosage. We are not concerned here with systemic therapy, but it does have some bearing on my subsequent remarks. Suffice it to say that physicians should not, under any circumstances, exceed a maximal daily dose (oral) of 15 mg. of prednisone or its equivalent and that they should strive for a maintenance dose of 10 mg. or less.

Equipment, Technic and Dosage

Besides a willing and cooperative patient, the only things that are necessary for local steroid injection therapy are a 2 cc. syringe and usually a 25 gauge needle, both of which have been autoclaved. We do not consider a simple needle stick an orthopedic surgical procedure and hence do not feel that operating-room technic is necessary, nor is it necessary for the physician to "scrub up" and put on sterile gloves. The site of injection is located (this will be discussed in detail later) and marked by a slight indentation of the skin with a fingernail. The area should be swabbed with an antiseptic, preferably bright-colored (mostly for psychic effect—on both physician and patient), and washed with alcohol. We have found that preliminary use of procaine is entirely unnecessary and merely subjects the patient to a second needle stick and adds additional time, slightly greater expense, and the risk of a procaine reaction. Following the steroid injection, a small patch is placed over the injection site and the patient is free to go about his business. He should be warned that occasionally there is mild to moderate accentuation of pain, which may persist for three to six hours or, rarely, even 12 hours.

Only hydrocortisone or one of its derivatives (meaning only corticosteroids with an OH at the 11-carbon atom) is effective at the tissue level. These substances would include hydrocortisone, prednisolone, triamcinolone, methylprednisolone and dexamethasone. It is noteworthy that the potency ratio between these substances is far less for local tissue effect than for oral systemic effect, but when proper dosage adjustments are made (approximately 5:3:3:3:1, respectively) the local tissue effect is identical. Thus, to minimize the general effects due to the systemic absorption of the locally injected steroid, I have come to favor hydrocortisone because 25 mg. of this substance will have far less systemic effect than 15 mg. of prednisolone or 5 mg. of dexamethasone.

In the past, it was strongly advocated that various insoluble salts of hydrocortisone or its analogs gave much longer beneficial action because the material remained in the joint and was not absorbed. For a while, I believed this too, but after considerable experience with comparative studies I am forced to conclude that a solution of hydrocortisone salt such as the phosphate will give a beneficial effect of the same degree for the same duration as the free alcohol suspension of the insoluble salt. Further, the solution offers the decided advantage that it can be injected through a needle with a much smaller bore than can the suspension. The smaller needle produces far less pain and trauma to the soft tissues, and there is less likelihood of trauma to the intraarticular structures, especially in the small joints of the fingers and hands. Both the solution and the suspension usually are prepared in strengths of 25 mg. per cubic centimeter for hydrocortisone, 10 mg. per cubic centimeter for prednisolone, and 4 mg. per cubic centimeter for dexamethasone.

At this point I must express the opinion that the instillation of hydrocortisone or one of its derivatives into an inflamed joint or soft-tissue area will bring about a blocking or inhibition of the inflammation within a matter of hours. The inflammation will then be abolished until a new stimulus or force sets up another inflammatory reaction, and this may be a matter of days, weeks, months or even years. For this reason, I believe that the steroid antiinflammatory action produced by local instillation is an *ad hoc* action and there is no continuing action whether solution or insoluble salt is used.

Dosage—Dosage may be expressed by considering the knee as a typical site for injection. One cubic centimeter of solution is quite adequate unless there is a large amount of effusion, in which case some of the effused fluid may be withdrawn and 2 cc. of solution replaced. One cubic centimeter or even 0.5 cc. may be sufficient for the elbow and the wrist, and proportionately smaller amounts are used for the metatarsophalangeal and metacarpophalangeal joints as well as the interphalangeal joints. Usually 2 cc. is injected into the hip joint. For extraarticular injections, 1 cc. is the usual amount instilled unless the area contains a large muscle like the gluteus, in which case 2 cc. may be desirable. Individual approaches to each joint and to the extraarticular areas will be discussed in detail later in this paper.

A word may be appropriate here about comparative effectiveness. Prior to the advent of local steroid injection therapy, procaine sometimes was used for injection into joints and frequently for instillation in cases of fibrositis. For the first few months after the institution of steroid injections, procaine continued to be used as a control. Its effect is so capricious and evanescent that no thoughtful clinician ever could seriously liken the action and effect of steroid and procaine.

Rheumatoid Arthritis

The intraarticular instillation of corticosteroids has facilitated greatly the general management of patients with rheumatoid arthritis. Sometimes the safe maximal oral dose may have quite satisfactory systemic effects but may not be adequate at the tissue level to impede inflammation in one or even several joints. Local instillation of steroids in these affected joints may reduce or even abolish such local inflammation, and the patient then may continue the otherwise effective general therapeutic program. Also, long experience in the management of patients with rheumatoid arthritis will lead the physician to expect that a majority of them will, at some time or another, have exacerbations of the disease, often affecting only one or a few joints. In such an instance, it may be a serious mistake to try to regain control of the disease by increasing the dose of systemic steroid, whereas the simple injection of steroid into the affected joints may permit continuance of the general program unchanged.

The duration of beneficial effect of steroid in rheumatoid joints is extremely variable, and in my experience there is no prognostic guidepost. The beneficial effect may last only a few days or a week, or it may last six months or longer or, occasionally, indefinitely. This variability applies not only to individual pa-

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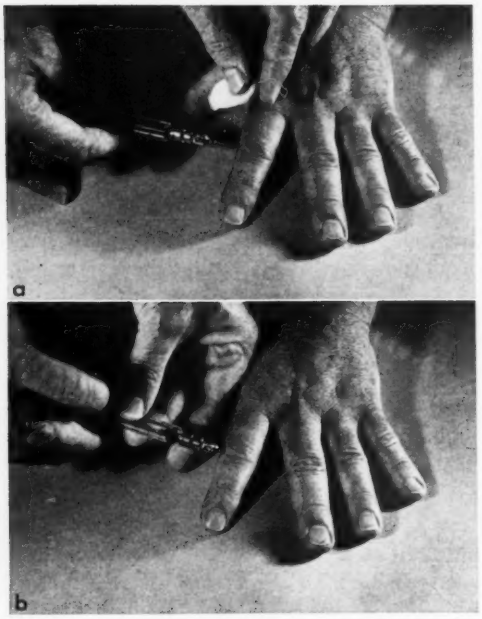

FIGURE 1. a. Acutely inflamed proximal interphalangeal joint of left index finger with the needle poised for injection.
b. The needle in the joint.

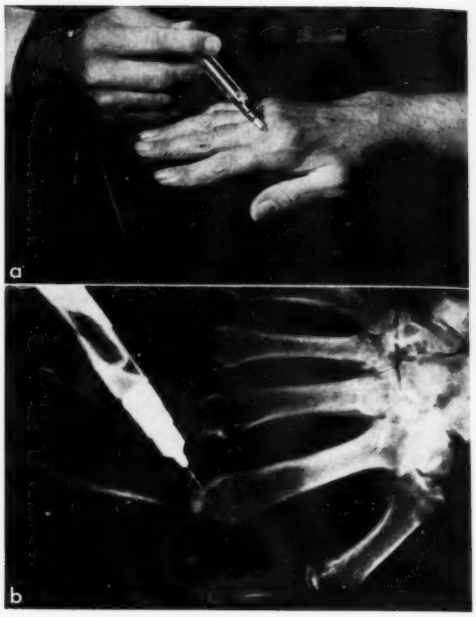

FIGURE 2. a. Rheumatoid metacarpophalangeal joint of right index finger with the needle in place and the injection proceeding.
b. X-ray of the joint with the needle in position.

tients but also to individual joints in the same patient and even to the same joint at different times. Until we can understand why a joint flares up with this acute inflammation, we will not know if, when, for how long, and why it will respond to intraarticular steroid injection. Further, in about 15 per cent of the rheumatoid joints injected with steroids there will be little or no beneficial effect. The speed of relapse of affected joints undoubtedly is influenced in part by local factors, especially trauma, and often it seems that when systemic exacerbation occurs a joint which has been gripped tenaciously by the rheumatoid disease for a long time is more likely to flare up than another joint which has not been involved previously.

I believe that all the joints of all four extremities are accessible and amenable to intraarticular instillation of steroid. The interphalangeal joints of the fingers are frequent sites of injection, and this is facilitated by using a very short 26 or 27 gauge needle and approaching the site from the dorsomedial or the dorsolateral angle (figure 1a and b). Only 0.1 or 0.2 cc. of the material is needed. I have injected as many as seven such joints in one patient at one sitting, and within 24 hours the functional capacity of the hands has been increased 60 to 70 per cent. The metacarpophalangeal (MCP) (figure 2a and b) and the metatarsophalangeal (MTP) joints also are frequent sites of injection; the same approach and the same needle size are used, but the amount of material usually is greater (0.2 or 0.3 cc.). The wrist joint may present some difficulty, and injection usually is made in the portion where swelling or tenderness is maximal, but always from the dorsal side. In the wrist, 0.5 cc. of the material is used, and the needle size may be increased to 25 gauge, although the smaller the needle the less trauma and the less pain produced. The elbow joint is easily approached between the articulations

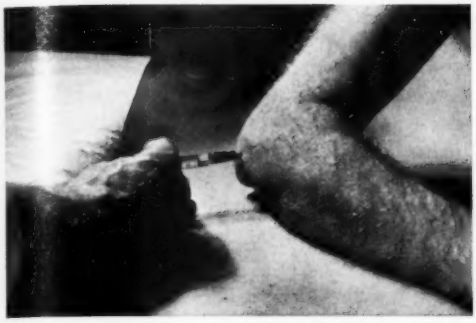

FIGURE 3. Needle in place in right elbow joint.

FIGURE 4. Injection being made in the right knee by the approach medial to the patellar tendon. Also shown is the left knee with a small patch over the site of an injection made at the same sitting.

of the radius and lateral epicondyle, inserting the needle in a triangle formed by these two bones with the ulna (figure 3). The topographic delineation can be enhanced considerably by having the joint held at a 90 degree angle and alternately supinating and pronating the forearm, with the palpating finger at the radiohumeral articulation. In the elbow joint, 1 cc. of solution is quite adequate and a 25 gauge needle is the proper size.

It is strange but true that the shoulder joint infrequently is involved with rheumatoid disease. Seldom is intraarticular injection in the shoulder joint indicated or worthwhile. If it is necessary, the joint can be approached posteriorly below the edge of the deltoid and triceps or anteriorly just lateral to the coracoid process.

The ankle joint is best approached with the patient supine. The needle is inserted from the anteromedial aspect about ¼ in. proximal to the tip of the medial malleolus. It can also be approached from the anterolateral aspect, using the same guidepost.

I have found that intraarticular injection of the knee is simplified by having the patient seated on the side of the table with the knee flexed to 90 degrees. By palpating the anteromedial aspect of the knee, the tibial plateau and the medial edge of the patellar tendon are located. The needle is inserted in the angle formed by the medial border of the patellar tendon and the tibial plateau, insertion being made obliquely posterior so that the needle point ends up behind the patellar tendon in the midline of the joint (figure 4). The approach may be made with only slightly more difficulty from the lateral side of the patellar tendon (figure 5a and b). Some authors have advocated a direct approach in the midline straight through the patellar tendon, but we have found that in many persons this tendon has extremely dense resistant tissue, and a much heavier needle of larger bore is required.

A significantly good result from local steroid injection may be expected in about 75 to 80 per cent of cases of rheumatoid articular involvement. Intraarticular steroid injection may be repeated however often it may be necessary. Occasionally one will find that local steroid injection of a joint produces a beneficial effect but with each succeeding injection the effectiveness seems to diminish. This waning effectiveness is observed in less than 10 per cent of cases, but it is surprising and inexplicable when it does happen.

The main consideration in regard to local steroid injection therapy in rheumatoid joints is that the general control and management of the disease are greatly facilitated thereby and simpler general measures can be sufficiently effective.

Osteoarthritis

It was only on a trial-and-error basis that we were willing to undertake local steroid injection of osteoarthritic joints. It must be frankly admitted that even this disease (more

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FIGURE 5. a. Injection being made in the right knee by an approach lateral to the patellar tendon. b. X-ray showing the needle in the joint space.

properly called degenerative joint disease) is not well understood, but it is generally regarded as a localized condition within the joint which does not reflect any systemic disease. All too often the diagnosis is made solely on the basis of the roentgenologic findings, and the reason for the clinical manifestations is not clear. Actually the diagnosis should be based more on clinical grounds and less on roentgenograms, for the roentgenologic finding of marginal calcific deposits, eburnation of the subchondral bone, and thinning of the joint cartilage often can be demonstrated in joints that are asymptomatic. It is not uncommon to observe these changes in both knees of a patient who has severe pain and disability in only one knee.

It may be presumed that the symptoms found in degenerative joint disease are the result of the trauma to the soft tissues produced by the roughened or needlelike calcific deposits acting against the soft tissues and sometimes even the synovial membrane. This gives rise to traumatic inflammation with swelling, which makes the condition more or less self-perpetuating because the swollen, inflamed soft tissues become even more vulnerable to this type of injury. If the synovial membrane is involved, a traumatic synovitis may result. Even joint effusion may appear, although this is unusual.

It is reasonable to expect that local injection of steroid would be highly beneficial in such a condition, and, in fact, it is very effective. The inflammation is inhibited, and the joint then remains functional until further trauma results in the recurrence of inflammation and disability.

The application of local steroid therapy in osteoarthritis is limited because the disease so often affects the joints of the vertebral column, which are, of course, inaccessible. The knees, however, are a common site of degenerative changes, and these joints have been injected quite frequently and with excellent results. The approach is much the same as that described for therapy of rheumatoid arthritis. Hip joints, too, frequently are the site of an osteoarthritic process, and the approach to these articulations is not too difficult. The needle may be inserted in the anterior aspect of the thigh at a point 1 in. below and 1 in. lateral to the midpoint of a line between the anterior spine and the pubic tubercle. The needle is inserted directly inward, and when it strikes the femoral neck it is withdrawn part way and then reinserted obliquely upward and inward. Injection of the hip also may be made from the lateral aspect with the patient lying on the side of the body opposite the involved hip, the approach being just above the greater trochanter, again following the neck of the femur until the joint cavity is reached. Injections have been made into numerous osteoarthritic hip joints and even into joints with the classic appearance of malum coxae senilis.

It has been said that repeated steroid injections into joints will allow undue use of the diseased joints and thereby result in more rapid destruction. This has not been true in our experience. In fact, we have found that the injections may be repeated many, many

times. To illustrate, a 62 year old man who has had osteoarthritis in both knees (figure 6) for many years, largely the result of genu varum, and who has worked as a manual laborer on an oil-drilling team all his life was first given injections of steroid into his knees in 1953 and has had them repeated at intervals of two to four months ever since, for a total of 24 such injections. When this therapy was started, his knees were so painful that he was hardly able to bear weight, and with each injection he has obtained complete relief and has returned to his job, carrying on for several months until the knees gradually became more and more painful. Then he would return for another series of intraarticular steroid injections.

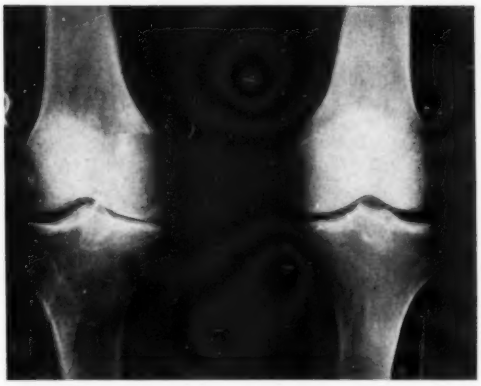

FIGURE 6. Recent roentgenogram of both knees of a man who works as a manual laborer and has had more than 20 injections into each knee joint over the past seven years. No ill effects are seen. The usual thinning of cartilage on the medial aspects, characteristic of genu varum, is apparent.

Fibrositis

Fibrositis is a poorly understood syndrome, but many rheumatologists consider it to be the most common of all rheumatic conditions. It is generally regarded as being benign and never productive of serious deformities or other sequelae (although this is not always true). There is no general agreement about the pathologic nature of the condition, but it would seem probable that there is some type of inflammatory reaction of a physicochemical rather than a cellular nature. Fibrositis can and does affect any soft tissue which is part of the skeletal framework or of the locomotor tissues. I believe it masquerades under a wide variety of names, most of which refer to a specific locality, e.g., tendonitis, epicondylitis, most cases of bursitis and neuritis, "painful heel," "painful shoulder," lumbago and many others. It would seem far better for clarity of thought and concept if all these terms were abandoned and if the clinician would restrict himself to the term "fibrositis" to designate this peculiar involvement of any one of these tissues.

The great problem in regard to fibrositis is the question as to whether it is primary or secondary and, if secondary, the nature of the underlying disease. Besides the primary generalized and localized types of fibrositis, there is the form that occurs as a part of every rheumatoid arthritic process and the form that sometimes occurs in association with osteoarthritis. Fibrositis also may develop as a result of trauma and may be an outward manifestation of a serious underlying disease such as metastatic cancer of the bone. The so-called shoulder-hand syndrome which often results from intrathoracic disease may well be essentially a fibrositis involving various portions of the shoulder girdle even though the pathologic mechanism here would seem to be a reflex sympathetic dystrophy. It is imperative, in any case of fibrositis, to make quite certain one is not dealing with some underlying malignancy or other serious disease.

Some common sites of fibrositis are the posterior cervical muscles, the muscles around the shoulder (especially in the deltoid just below the acromion), and the central portion of the muscles attached to the lower half of the scapula below the spine (figure 7), and also the bicipital groove. Occasionally the entire distribution of the pectoralis muscle may be involved. The paraspinal muscles throughout the vertebral column are notorious for their fibrositic involvement, and at any level. The subscapular muscles often become involved with fibrositis, and the gluteal region is an extremely common site of involvement. In the latter there is exquisite tenderness in the glu-

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FIGURE 7. Injection being made into the central point of fibrositis involving the infraspinous muscles overlying the left scapula.

FIGURE 8. Injection being made into the medial epicondyle at the attachments of flexor muscles on left arm.

teal attachments to the ileum just lateral to the sacroiliac joint. Occasionally there is also some fibrositic involvement of the musculotendinous attachments at the medial condyle of the knee. I have seen severe fibrositis involving the anterior calf muscles as well as the belly of the gastrocnemius muscle just at the point where it crosses the knee posteriorly.

The area of the most exquisite tenderness is located by palpating with one finger. This area may be only 2 cm. in diameter. The amount of material injected may vary from 0.5 to 2 cc. depending on the extent of soft-tissue involvement. The needle is inserted to a considerable depth and the material is injected gradually as the needle is withdrawn, so that all fascial layers will be infiltrated with the steroid. After withdrawal of the needle, a dry cotton ball is applied at the injection site and the area is massaged vigorously to insure distribution of the steroid through the tissues.

A thorough understanding of fibrositis is not possible at present, but it is well to have a thorough appreciation of its clinical significance (meaning its ubiquity and its ability to mimic many other types of pain, usually of a more serious nature). This appreciation is made even more difficult because of the very common characteristic of radiated or referred pain from an area of fibrositic involvement. For example, involvement of the shoulder girdle may not be manifested by pain in the shoulder but may produce as the chief complaints numbness, weakness and disability of the hands. Fibrositic involvement of the muscular attachments to the medial condyle (figure 8) and the lateral epicondyle (figure 9) often gives rise to an ache in the hand corresponding to this general muscular distribution. Gluteal fibrositis (figure 10) usually is manifested clinically by deep-seated aching in the thigh. Fibrositic involvement around the scapula or the paraspinal muscles often gives rise to referred dull aching or pain in the anterior corresponding segments.

Special situations of local steroid therapy also may be cited. I have seen a number of patients with an acutely painful heel who had so much pain and tenderness on the plantar surface of the heel that weight bearing was impossible and who obtained complete relief within a few hours after local injection of steroid into the painful area. Moreover, on a number of occasions a patient has complained of persistent pain in a knee which did not respond to one or several injections of steroid into the knee joint proper, and careful examination failed to disclose tenderness or evidence of inflammation within the joint but revealed an acutely painful and tender area of fibrositis involving the musculotendinous attachment at the medial femoral condyle. Infiltration of this area with steroid may produce prompt relief of the pain (figure 11). This effect may be truly dramatic to a patient who has had continuous pain in the knee for many months and has not obtained benefit from *intra*articular injections.

FIGURE 9. Injection being made into an area of fibrositis (tennis elbow) at the attachments of the extensors to the left lateral epicondyle.

FIGURE 10. Injection being made into an area of gluteal fibrositis on the left side. Care should be taken to massage the area of injection vigorously to diffuse the material through the tissues for maximal local benefit.

Injections into posterior cervical fibrositic areas usually are not feasible, but if the area of involvement is small and sharply circumscribed an injection may be tried. Tenderness and pain in the tensor fascia lata may respond well to injection. Local steroid injections also have been made in muscles of the chest wall, anterior tibial muscles, temporal muscles, and various fasciae and ligaments, and even the anterior abdominal wall and sometimes the periosteum.

Complications

Infection has long been feared as the most dreaded complication of intraarticular injections, because it was a common belief that joint tissue was a fertile field for bacterial growth and had little resistance to bacterial invasion. After 10 years' experience with intraarticular instillation, it would seem not only that this old belief is not true but that the real situation more likely is exactly the opposite. Hollander has reported only 12 infections in 100,000 joint injections, and only two of these 12 infections occurred among the last 40,000 injections, which were made after autoclaving of syringes and needles became a routine practice. At the Columbus Medical Center, we have been fortunate in that not a single infection of a joint has occurred, and only one instance of soft-tissue suppuration has followed steroid instillation. I think this incidence must be regarded as considerably lower than that of infection following any other type of subcutaneous or intramuscular injection. Of course, if infection does develop, every attempt should be made to recognize it early so that intensive therapy can be instituted. Generally speaking, it would seem that infection is a remote and rare complication of intraarticular steroid therapy.

Exacerbation of pain probably should be listed as a complication, although it is not a serious clinical problem. About 10 to 20 per cent of all intraarticular injections produce a temporary increase in pain in the joint lasting three to six hours and sometimes as long as 12 hours. Very occasionally this exacerbation of pain may be quite intense and necessitate the use of codeine. However, in the vast majority of cases if the patient is forewarned of

FIGURE 11. Injection being made in the *extra*articular tissues involved with fibrositis above the medial condyle of the left knee.

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the possibility and assured in advance that it is of no serious consequence, it usually does not pose a problem in clinical management. The reason for the exacerbation of pain is not known but it does not seem to be related to the effectiveness of the injection.

The development of instability of the joint due to ligamentous relaxation is a rare complication limited to rheumatoid joints. It apparently occurs in joints in which there has been excessive effusion or prolonged inflammation and the ligaments have been stretched unduly for a prolonged period. Following the injection of steroid, the inflammation subsides and the joint effusion disappears, and the relaxed ligaments and atrophied muscles allow some subluxation of the joint. In some instances, physical therapy with passive and active muscle exercises to increase the tone of the muscles that cross the joint is urgently indicated. It should be remembered that the strength of a joint depends largely on the tone and quality of the muscles that cross it. It has been reported that in a few cases in which instability of the joint was very severe, arthrodesis was necessary. We have not been confronted with such a complication.

In my experience it is highly desirable but not imperative to inject the solution into the intrasynovial space. The physician need not be concerned or alarmed if some or all of the material is injected outside this space, for certainly no harm results. The beneficial effect of the injection will, of course, be less, but there can be no doubt that some benefit will accrue even in this case; apparently this is because of diffusion through the soft tissues into the synovial lining.

1961

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ALLAN C. BARNES, M.D.

Professor and Chairman, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore

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Congestive Heart Failure

ITS PHYSIOPATHOLOGY AND TREATMENT, WITH SPECIAL REFERENCE TO INTRACTABLE HEART FAILURE

WILLIAM H. MORSE AND RICHARD J. BING*

Wayne State University College of Medicine, Detroit

The relationship between the physiopathologic factors involved in heart failure and the manifestations of the disease is not clearly understood. Clinical signs and symptoms are caused by disturbances in electrolyte and water balance.

Speculative theories have been advanced concerning the role in heart failure played by cardiac metabolic disturbances, changes in the molecular structure of actomyosin, excretion of aldosterone, release of antidiuretic hormone, and perversion of the normal mechanisms of both fluid volume and sodium regulation.

Treatment of congestive failure is still chiefly empiric, consisting of careful regulation of sodium and water intake and administration of digitalis and diuretics.

HEART failure, a condition known to man for hundreds of years, is still a mysterious ailment. The mystery results from the difficulties in relating the factors involved in its production to the multiple manifestations of the disease. Although the heart is the organ primarily involved, the clinical signs and symptoms result from disturbances in electrolyte and water balance. In addition to the heart, the kidneys, the adrenals and the pituitary play important roles. It is the purpose of this discussion to outline the physiopathology and treatment of this disease and to deal with its clinical manifestations and their basic mechanisms.

Physiopathology of Congestive Failure

Cardiac metabolism—It is a curious fact that in most types of heart failure anatomic as well as biochemical disturbances within the heart muscle are absent.[1] Yet, there is certainly enough evidence that the heart muscle is seriously affected; cardiac enlargement and hypertrophy occur and are frequently followed by dilatation. In normal individuals, the heart extracts glucose, pyruvate, lactate, amino acids, fatty acids and ketones.[1] In most types

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RICHARD J. BING

of chronic congestive failure due to hypertensive, valvular or arteriosclerotic heart disease, the myocardial uptake of these substrates and of oxygen is not altered.[1] This has suggested that the underlying defect in the heart muscle may be located in utilization rather than in production of energy.[1] It should be kept in mind that this theory is arrived at primarily by exclusion.

However, some types of heart failure, such as those resulting from anemia, anoxia, hyperthyroidism or beriberi, are certainly due to metabolic disturbance.[1] In anemia, the oxygen-carrying capacity of the blood is diminished, and it has been demonstrated that when the hematocrit is reduced to a level of 24 to 31 per cent there is a depression of ventricular function curves. This loss of the heart's ability to increase its work occurs when the coronary bed is near maximal dilatation, suggesting that despite coronary vasodilatation, delivery of oxygen to the myocardium is inadequate. In anoxia, there is a rapid diminution in phosphocreatine, adenosinetriphosphate and glycogen, while the level of hexosemonophosphate increases.[1] These changes are compatible with rapidly progressing glycolysis and suggest that under these conditions there are disturbances in the enzyme system in heart muscle which are similar to those encountered in skeletal muscle. Even brief anoxia, as present during angina pectoris or in localized anoxia resulting from coronary occlusion, results in glycolysis in the myocardium. The changes in myocardial metabolism in hemorrhagic shock are similar. Myocardial infarction also leads to acute myocardial failure if the uninvolved portion of the myocardium fails to compensate for the loss of contractile power of the ischemic muscle.[1]

Thyrotoxicosis is frequently associated with congestive failure, but the failure may be reversed following adequate therapy. It is likely that the oxygen consumption of the heart is increased in this condition.[1] Apparently, the organelles of energy production, the mitochondria, are particularly susceptible to the effect of the hormone, and failure of oxidative phosphorylation has been observed to result from an overproduction of thyroid hormones.

Beriberi heart is probably the one type of heart failure in which a metabolic failure can be pinpointed with a certain degree of accuracy. It is known that thiamine pyrophosphate catalyzes the reactions of pyruvate to coenzyme A and of alpha-ketoglutarate to succinate, as well as the transketolase reaction. The heart muscle, therefore, like any other tissue, is unable to utilize lactate and pyruvate normally. In dogs with thiamine deficiency at low rates of coronary blood flow, the myocardial oxygen extraction is high, and at larger flow the oxygen content of coronary sinus blood is elevated.[1]

Dynamic considerations—Heart failure results in a different relationship between the filling pressure (diastolic or initial tension) and the work of the heart. This first was shown by Starling.[2] The heart performs differently when it is failing, or, as Starling pointed out, it has a different "tone." A heart that is "fresh" and a heart that is "tired" are not on the same performance curve.[2] The question as to the cause of the difference in the cardiac tone remains to be explained. It may be speculated that the altered performance of the heart is the result of changes occurring in the molecular structure of the contractile protein complex actomyosin.[3]

Regulation of sodium and water balance—How does myocardial failure produce the clinical manifestations of heart failure? What is the link between the failing myocardium and edema? It is necessary here to examine the regulation of extracellular fluid and sodium balance.

There is still no agreement on the mecha-

nism with which the kidney handles sodium; ideas change as rapidly as papers on this subject roll off the press. It is now believed that concentration of urine occurs with the help of a countercurrent system in Henle's loop and in the capillary loops of the renal medulla.[4] The transport of sodium chloride from the lumen of the thick ascending limb of the loop into the interstitial space and hence, by diffusion, into the descending loop supplies the motive force. Therefore, all the tubules in the interstitial space in the renal medulla have a hypertonic content. The fluid from the collecting tubes which passes through this hypertonic environment loses water by osmosis, resulting in the production of hypertonic urine.

What factors regulate the quantity of sodium reabsorbed? It has been thought that the glomerular filtration rate is the rate-limiting factor, but sodium reabsorption by the tubules, as regulated by endocrinic and neurogenic influences, appears to be more important.[5]

Aldosterone—Aldosterone, a recent newcomer in the series of adrenal steroids, greatly influences excretion of renal sodium and potassium. Luetscher and Curtis[6] noted that in patients with nephrosis and heart failure, aldosterone excretion in the urine was elevated in sodium deprivation and potassium loading and decreased in the reverse states. They also demonstrated that hypophysectomy had little influence on aldosterone excretion, thus placing control elsewhere.

It has been demonstrated that aldosterone secretion may be influenced by the venous pressure.[7] For example, constriction of the inferior vena cava above the diaphragm leads to an increased secretion of aldosterone, and a release of the constriction results in a decrease. The fall is blocked by bilateral vagal section, implicating other modes of control. In addition, neural factors may play a role in conservation of renal sodium. Barger[5] found that intrarenal perfusion of sympathetic-blocking agents results in an increase in sodium and water excretion. Stripping of carotid sinus and aortic arch receptors results in increased peripheral sympathetic activity, causing antidiuresis.[8] It is known that a fall in blood volume (or simulation of a fall in blood volume, as in low-output failure) leads to increased aldosterone secretion in dogs, and that this rise is blocked after bilateral splanchnicectomy has been performed.[9]

The factors controlling the physiologic action of aldosterone may be summarized as follows: Aldosterone secretion may be partially under the influence of ACTH.[10] Sodium deprivation results in increased urinary excretion of aldosterone and probably in an increased secretion by the adrenals. Potassium retention may follow loss of sodium, and this may in turn serve to elevate aldosterone secretion. Increase in the pressure in the inferior vena cava above the level of the renal veins produces an increase in aldosterone secretion.[7]

Antidiuretic hormone—In a normal person a continually fluctuating release of antidiuretic hormone (ADH) serves homeostasis by regulating the renal tubular reabsorption of water in accord with the concurrent needs of the organism.[11] Under normal conditions, there is a suppression of ADH secretion by the pituitary if the body fluid volume increases. This is probably the case, but few advances have been made in elucidating the mechanism by which this is accomplished. It has been known for a long time that the changes in blood volume can be accompanied by alterations in urine flow. Small diminutions in plasma volume can lead to oliguria, and small transfusions can lead to diuresis.[11] ADH is released in response to a decrease in the effective osmotic pressure of the extracellular fluid, in response to a decrease in the effective extracellular fluid volume, and in response to a variety of physiologic stimuli, pharmacologic agents, and physiologically active substances. There is now available a fairly large body of evidence indicating that the supraopticohypophyseal system is responsive to some factor or factors associated with the change in the volume of the extracellular fluid in some critical area of the body.[11] A reflex arc with a receptor organ and an afferent and efferent reflex arc has been suggested in the regulation of ADH release. Sieker, Gauer and Henry[12] found that application of negative-pressure breathing in man produced an increase in urine excretion.

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In contrast, positive-pressure breathing diminished urine flow. Neither urine pH nor sodium and potassium excretion changed, suggesting that this was indeed a true water diuresis. It appears likely that the receptors responsible for this phenomenon are located in the left atrium.[13]

Water and salt in congestive failure—If there were no disturbances in the homeostatic mechanism, an acute decrease in whole blood volume should result in enhanced renal tubular reabsorption of sodium; an increase in whole blood volume should have the opposite effect. This is not so in congestive heart failure. In this condition a perversion of the normal regulatory volume mechanisms has occurred. In congestive heart failure there is both retention of sodium and an even more disproportionate retention of body fluids, leading to edema. There is now ample evidence that both edematous and nonedematous cardiac patients have an increase over the normal amount of exchangeable sodium in relation to total body water.

Farber and Soberman,[14] using antipyrine space as a measure of total body water, have shown that both edematous and nonedematous cardiac patients have an increase in exchangeable sodium (Na_{24}) in relation to total body water, as compared with that in normal persons and in patients with edema caused by renal and hepatic conditions. They conclude that due to limited cellular permeability to sodium this aberration may be caused by (1) an increase in extracellular fluid with intracellular dehydration or (2) an absolute increase in total body sodium.

Aikawa and Fitz,[15] by measuring changes in exchangeable sodium and "sodium space" with isotope-labeled sodium during diuresis, noted a decrease in weight (water) exceeding that expected on the basis of fall in the above parameters. They imply that this phenomenon is due to a decrease in volume of the intracellular compartment.

Cort and Maxwell[16] noted an intracellular potassium deficit in treated cardiac patients which was associated with an increase in intracellular water and sodium. This also was relieved with administration of potassium salts, which resulted in natriuresis and diuresis. In heart failure the mechanisms of both volume and sodium regulation are out of order.

Aldosterone and congestive failure—Increased secretion of aldosterone alone, such as in primary aldosteronism, does not produce edema.[5] Furthermore, increased aldosterone excretion has not been observed in all cases of congestive failure.[5] Direct infusion of aldosterone into one renal artery of a normal dog produces no retention of sodium but results in potassium diuresis.[5] It may be true that the kidneys in congestive failure are more sensitive to mineralocorticoids. It certainly has been shown that intrarenal infusion of aldosterone in dogs with valvular damage leads to increased potassium secretion and decreased sodium excretion.[13] However, the role of aldosterone in congestive failure is by no means clear. Even if it could be demonstrated that aldosterone secretion in congestive failure is increased, it still would leave us in the dark as to the mechanisms which are responsible for the increased aldosterone secretion in the presence of increased body fluids. Pressoreceptor nerves play a role in the regulation of aldosterone secretion; thus, this mechanism may be responsible in congestive failure for both sympathetic activity of the kidneys and the increased aldosterone secretion from the adrenal cortex, but as yet there is no proof of this in man.[8] Another factor of note, particularly in intractable dropsy, is that other adrenal steroids may be diminished. In such cases aldosterone may be normal, suggesting that the aldosterone to glucocorticoid ratio, rather than the absolute aldosterone level, may be the thermostat in edema formation. It is well known that adrenal atrophy may be present in terminal congestive failure, which would tend to support this concept.[17]

ADH and congestive failure—The situation pertaining to the secretion of ADH is equally unsettled. There is no proof that secretion of ADH is increased in congestive failure. Under normal physiologic conditions, an increase in the body fluids leads to a diminution in posterior pituitary secretion. In heart failure, this regulatory mechanism does not function. The assumption has been made that in heart failure

the distribution of volume compartments is such that there is a decrease in some critical area.[11] All reports which purport to demonstrate large amounts of ADH in the urine in diseases associated with edema must be viewed with caution.[11]

Treatment of Congestive Failure

The physician cannot wait until all these controversies are settled. He must treat the patient to the best of his ability, using physiologic principles and clinical judgment. Much of the treatment remains empiric. The mainstays of treatment in congestive failure are administration of digitalis and diuretics and careful regulation of sodium and water intake.

The mechanism of the action of digitalis remains a mystery.[18,19] We have learned so far that cardiac glycosides act chiefly on the heart rather than on the kidney, and that in all likelihood they act on the contractile elements of the heart muscle by regulating the sodium and potassium concentration within the cell. The latter effect is responsible for the electrocardiographic alterations seen following the injection of the glycoside. There is as yet no answer on how cardiac glycosides affect contractility of the heart muscle.

For practical purposes there is not much difference between individual digitalis preparations. It is important that the physician thoroughly understands the clinical effects of the preparation he uses. It should be remembered, however, that no strict rules can be made regarding digitalization or maintenance dosages, and that each individual must be treated according to his own reactivity to the drug. Older people may be more sensitive to digitalis. In actual practice, aversion to food is usually the first sign of digitalization.[20] When rapid digitalization is required, many physicians prefer lanatoside C, which may be given in a dose of 0.4 or 0.8 mg. If there is doubt as to whether or not a patient has already received the drug, 0.4 mg. CEDILANID® in 50 cc. of glucose and water may be administered intravenously by drip over a period of 15 minutes. When congestive failure persists despite therapy, the possibility of inadequate digitalization must be considered. If digitalis toxicity occurs, a potassium salt such as potassium citrate or potassium chloride (2 gm. two to three times daily) may be beneficial.

All diuretics produce changes in electrolyte and fluid balance which the physician must consider. Thus, mercurial diuretics often result in hypochloremic alkalosis. Hyperchloremic acidosis may follow the ingestion of ammonium chloride or carbonic anhydrase inhibitors. Hyponatremia may result from mercurial diuretics and may be common in severe advanced heart failure. The chlorothiazide drugs, effective when orally administered, have sufficient advantage to make them desirable for long-term treatment and for treatment between injections of mercurial diuretics.[20] Chlorothiazide is most commonly given in doses of 500 mg. once or twice daily. When the use of these drugs is prolonged, it is wise to omit diuretics two days each week or to prescribe them on alternate days. Chlorothiazide is accompanied by potassium depletion more often than are mercurials. This is especially likely to occur in patients having anorexia or diarrhea and in those receiving corticosteroid therapy at the same time. It is not likely that hydrochlorothiazide produces a significantly smaller loss of potassium than does chlorothiazide. The physician should keep in mind that hyperuricemia has frequently been noted following administration of these drugs.

A low-sodium diet remains one of the more important features in the treatment of congestive heart failure. In severe congestive failure only 200 to 300 mg. of sodium should be allowed per day.[21] This is particularly true in intractable heart failure. However, rigid restriction of sodium may lead to hyponatremia with its resulting symptomatology. Milk or milk substitutes represent a good diet that is low in sodium.[20]

The administration of potent diuretics is fraught with danger in the presence of active nephritis. In such instances, the mercurial diuretics are contraindicated, but small daily doses of chlorothiazide (500 mg.) may be given and the effects noted on urinary output.

To the armamentarium of the physician has

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now been added a series of new compounds which show antialdosterone activity. They are the steroidal 1-17 spirolactones. There is substantial evidence that these compounds in animals act as inhibitors of aldosterone.[22] They have no action on adrenalectomized animals without replacement therapy, but in such animals the drugs antagonize the effects of injected desoxycorticosterone acetate and aldosterone, inhibiting both the sodium-retaining and the potassium-losing effects. In man a similar situation pertains. In adrenalectomized patients the spirolactones are ineffective. However, when replacement therapy is given, the effects of desoxycorticosterone are inhibited, increasing excretion of water, sodium and chloride and decreasing excretion of potassium, phosphate and ammonia. Normal subjects on high sodium intake are unaffected by the spirolactones, but, when high urinary output of aldosterone is induced by feeding a low-sodium diet, they respond to the spirolactones in the same manner as Addisonian patients receiving steroids. The findings suggest that the drug is a peripheral inhibitor of aldosterone and does not affect the production by the adrenals of aldosterone or other hormones.

Refractory Heart Failure

Refractory heart failure may result from irreparable damage to the heart muscle. In such a case the problem may well be unsolvable. This is primarily the case in the late stages of rheumatic heart disease with multivalvular diseases.

On the other hand, intractable heart failure may be the result of correctable heart disease. In this group belongs high-output failure due to hyperthyroidism, anemia, beriberi, arteriovenous fistula and certain types of congenital malformations such as atrial or ventricular septal defect, aortic pulmonary window, or large patent ductus arteriosus. Medical or surgical treatment of the underlying condition will remedy the failure.

Intractable heart failure may also be the fault of the physician. Overdigitalization and hyponatremia induced by the combination of diuretics and low salt intake belong in this group. Mercurial diuretics suppress the reabsorption of sodium into the renal tubules, and an equivalent amount of water accompanies the unreabsorbed sodium en route down the course of the nephron.[21] With a contraction in volume evoked by the diuretic, the volume control system becomes activated to a greater degree. The typical patient with advanced heart failure is on a low-salt diet. However, water is permitted as desired. Consequently, positive sodium balance does occur, and reexpansion of volume occurs with a further decrease in plasma sodium concentration. Hypochloremic alkalosis ensues, and the presence of decreased concentration of sodium renders mercurial diuretics ineffectual. The clinical abnormalities encountered in this condition are well known. They include central nervous system abnormalities with apathy, drowsiness, confusion, psychosis and coma. There are gastrointestinal derangements with anorexia, nausea, vomiting and cramps. There is muscular weakness accompanied by cramps and twitching. In the patient with severe congestive heart failure in whom hyponatremia develops, the glomerular filtration rate decreases as a consequence of the failure and the action of the volume control system. Therefore, one frequently finds a rising blood urea nitrogen level in the patient with a progressively decreasing sodium concentration.

The treatment of hyponatremia is a delicate one. The fact that hypervolemia is already severe suggests that any further expansion of volume must be avoided. Administration of hypertonic saline is distinctly contraindicated, since it may lead to further expanding volume and to precipitation of fatal pulmonary edema. Therefore, plasma sodium concentration must be raised without further expanding volume and without adding more sodium. Thus, the principal attention must be focused on total body water. The patient should be placed on a rigidly restricted fluid intake, generally in the vicinity of 800 cc. per day. Because of the loss of water through insensible routes as well as that amount excreted in the urine, the patient will gradually contract his total body water and particularly his extracellular fluid volume. A modest increment in salt intake of approximately 2 to 3 gm. per day may be

employed in association with water deprivation. With this treatment, improvement does not immediately occur. The patient may become increasingly restless and thirsty, and the symptoms may be accentuated. Moreover, the sodium concentration may actually fall. After the third day, however, improvement begins, and by the end of the week the sodium concentration is generally increased. Once this has been accomplished, the patient may be expected to respond to diuretics again. However, if the patient then is permitted water ad lib., the same chemical abnormalities will develop again. It therefore is mandatory to maintain him on a restricted water intake. The rigidity of restriction depends on serial measurements of sodium concentration.

Another method of treating intractable cardiac disease has received attention in recent years following the work of Camara and Schemm [23] with ACTH. They reported on the use of this hormone in 21 patients with intractable edema. Seventeen of these patients sustained clinical benefit following its use in a daily dosage of 40 to 100 units for 10 to 12 consecutive days. Four patients had diuresis during administration, three immediately following cessation of therapy, and 10 exhibited an increase in sensitivity to mercurial diuretics. Various explanations were considered. This condition is not likely due to alteration in the glomerular filtration rate, since in nephrotic patients this is not at all correlated with sodium excretion or absorption, although the mechanism of edema in nephrosis may differ from that in cardiac failure.[14] It may stimulate secretion of an antidesoxycorticosterone hormone, depress endogenous desoxycorticosterone, or primarily improve myocardial function, although there is no convincing evidence of this. Administration of adrenal steroids may furnish exogenous hormones lacking in the patient with terminal cardiac disease.[24] Some other clinical studies[25,26] have shown improvement in intractable cardiac disease, as manifested by increase in sodium, potassium and chloride excretion. These observations would seem to justify clinical trial of corticosteroids in patients with refractory heart failure.

Finally, intractable heart failure may be due to insufficient sodium restriction. In the absence of hyponatremia, it is imperative that the patient in refractory heart failure be placed on a diet very low in sodium (200 to 300 mg. of sodium per day).[20]

Comment

This discussion has stressed the vast amount of unknown territory within the continent of congestive heart failure. As so often happens in medicine, successful treatment has advanced before the physiopathology is understood. It is quite clear, however, that further progress will depend to a large extent on further insight into the mechanism of this disease.

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1961

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

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Cancer of the Breast: Varying Views of Treatment

GEORGE CRILE, JR., M.D.

Head, Department of General Surgery, Cleveland Clinic, Cleveland

For many years, radical mastectomy has been performed routinely for breast cancer when clinical examination has revealed the lesion to be operable. However, recent studies have indicated that simple mastectomy may be the treatment of choice in breast cancer that has not metastasized to the axilla and that radical mastectomy is futile in the presence of extensive invasion of the upper axilla. Therefore, axillary exploration prior to commitment to radical mastectomy seems a logical procedure. This discussion will cover the various types of procedures indicated according to the findings of axillary exploration.

Complete program available by writing to Dr. E. S. Hamilton, Program Chairman, Box 1109, Madison 1, Wisconsin.

Coccidioidomycosis: A Primer

MARCO BRUSCHI

Bakersfield, California

The evolution of knowledge concerning coccidioidomycosis is summarized, and the geographical distribution of the disease is outlined. The life cycle of the causative organism, the natural course of the disease, and the manifestations of both the primary type and the progressive or disseminated form are presented. Gross and microscopic changes produced by the infection and various tests to aid in diagnosis are described. Indications for surgical treatment are given. Medical therapy of disseminated coccidioidomycosis has been disappointing, but amphotericin B shows some promise.

MARCO BRUSCHI

In 1892 Posadas and Wernicke[1-3] in Buenos Aires reported the first case of coccidioidomycosis. In 1896 Rixford and Gilchrist[4] produced local lesions in animals from the first case of the disease reported in the United States. Ophuls and Moffitt[5] in 1900 outlined the life cycle of *Coccidioides immitis*. In 1914 Cooke[6] developed a precipitin test, and in 1915 Dickson[7] thoroughly described the coccidioidal granuloma in a series of disseminated cases. Hirsch[8] in 1927 demonstrated coccidioidin skin sensitivity. Giltner[9] in 1918 and Beck[10] in 1929 described the infection in farm animals. In 1929 Ophuls, discussing a report by Pulford and Larson,[11] showed the lungs to be the portal of entry for the disease, which he had suspected in 1905.[12]

Dickson and Gifford[13] in 1938 noted the relationship of the antecedent erythema nodosum and the primary type of coccidioidomycosis; prior to this, the disease had always been described as disseminated. In 1939 Smith[14] reported a survey on valley fever in the San Joaquin Valley. Winn[15] in 1941 described the residual pulmonary cavitation. Emmons[16] in 1942 discovered the disease among rodents. In 1946 Smith and associates[17,18] pointed out the importance of dust control in suppression of the disease, and at this time the complement-fixation test for use in dis-

Adapted from the author's motion-picture film, "Coccidioidomycosis," which is available from the American Medical Association.

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FIGURE 1. Geographical distribution of coccidioidomycosis. The pins with white circles designate the endemic area, and those with white stripes the areas to which the disease has been transmitted by fomites.

seminated coccidioidomycosis was developed. Forbus and Bestebreurtje[19] in 1946 reported the pathologic findings in a large number of cases, and Puckett[20] in 1954 pointed out the hyphal forms in the human host.

Cohen, Miller, Bos, Webb, O'Connor and Egeberg[21-30] have tested numerous drugs in a search for a means of treatment of the disseminated disease. Huntington[31-33] has furthered our knowledge of the histopathologic aspects, and Birsner and Smart[34,35] have reported the roentgenologic findings in both the primary and disseminated types. Levan[36] has cited the industrial implications as well as the importance of fomites in transmission of the disease.

Geographical Distribution

Coccidioidomycosis, a fungous disease caused by *C. immitis,* is endemic in the arid southwestern part of the United States. The general endemic area includes the southern San Joaquin Valley and other parts of southern California, western Texas, southern and central Arizona, and the southern parts of New Mexico, Utah and Nevada. Recent studies reveal an increase in incidence in this general endemic area but a lower incidence in the extended zone;[37] this change in the area corresponds roughly with that found in the Lower Sonoran life zone.[38] The increased incidence may be due both to an increase in population and to availability of diagnostic tools for the informed physician. The endemic area (figure 1) does not stop at the Mexican border; the disease is found in Mexico, Central America and South America. Moreover, it has been found in almost every state of the United States among persons who have traveled in the endemic area.[39] The disease has been transmitted by fomites to Hawaii, southern California, the southern and northeastern parts of the United States, Canada, Italy and the Balkan countries.[36]

The United States Air Force conducted two important groups of studies on the disease in the mid-1940s[17] and in the middle and late 1950s.[40,41] The studies during World War II,

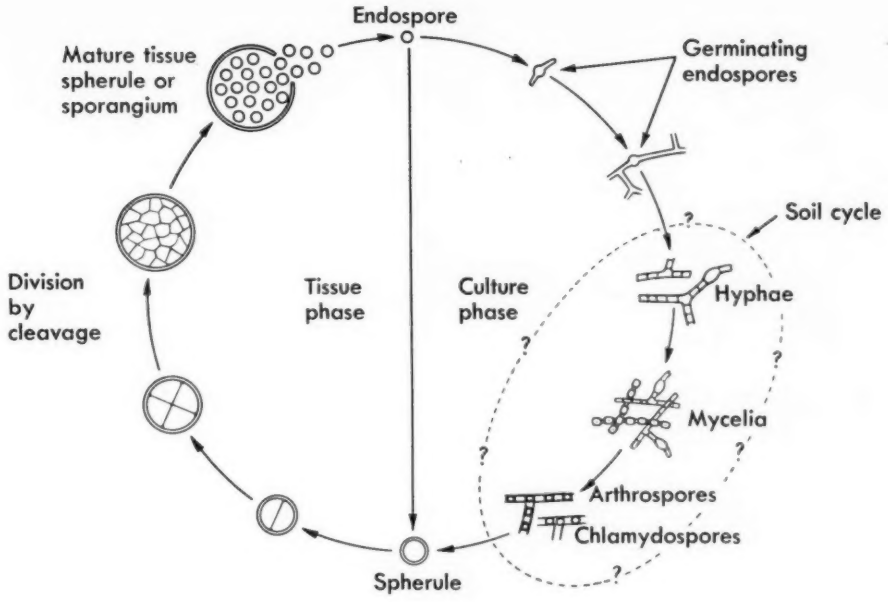

FIGURE 2. Life cycle of *C. immitis*.

Prepared with the assistance of M. Biddle, Los Angeles.

at Minter and Gardner Air Fields in Kern County, Lemoore Air Base in Kings County, and Castle Field in Merced (all in California), showed the rapidity with which large groups of nonimmune men became infected and also revealed that dust control reduced the infections by about 55 per cent. The more recent studies by the Air Force, conducted in Arizona, revealed that 23 per cent of newly arrived airmen became positive reactors to the coccidioidin skin test in one year. The number of man-days lost per year as a result of coccidioidomycosis almost equaled total man-days lost because of upper respiratory infections, pneumonia, infectious mononucleosis and traumatic injuries combined. Skin testing demonstrated the tapering off of the endemic area from Arizona to central Texas.

Life Cycle of C. immitis

The life cycle of *C. immitis* is divided into the culture (saprophytic) phase and the tissue phase[42] (figure 2). In the culture phase the endospores germinate to become branching filaments or hyphae. Matted hyphae are known as mycelia. Rectangular arthrospores develop and rupture from the hyphae. We suspect, but are not certain, that there is a "soil cycle" in which the hyphae, mycelia and arthrospores develop in infected soil.

In the tissue phase, after inhalation of the arthrospores by the human or animal host, *C. immitis* appears in the tissues as a round, doubly refractive structure commonly called the spherule, whose cytoplasm divides to form endospores. The mature spherule, with endospores, is the sporangium. When the sporangium ruptures, each endospore develops into a new spherule and the tissue phase of the cycle is repeated within the host. However, hyphae have been noted in coccidioidal pulmonary cavities, meninges and granulomas, and spherules have been developed in vitro from mycelia under controlled laboratory conditions.[19,43,44]

In the Lower Sonoran life zone, temperature and moisture conditions are such that endospores in the soil may develop into

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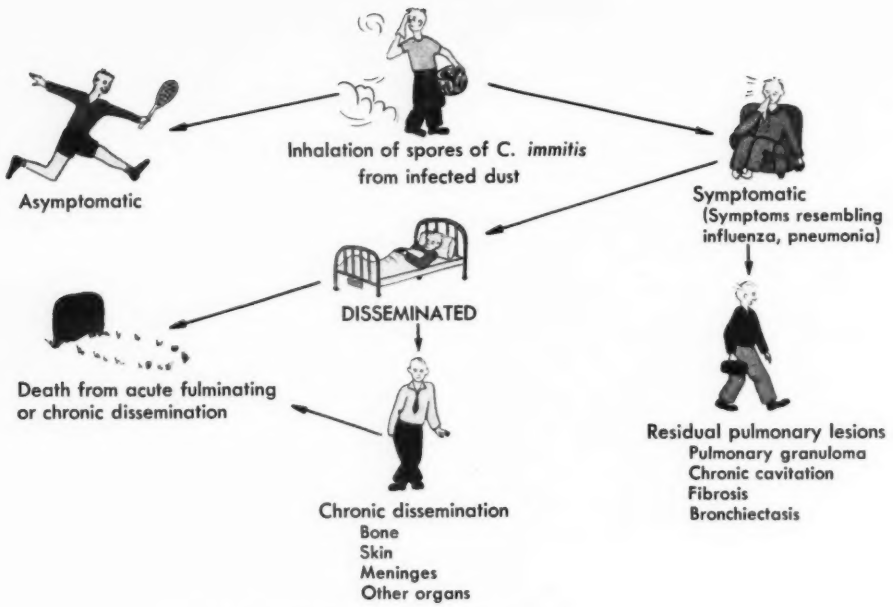

FIGURE 3. Natural course of coccidioidal infection.
From the original diagram by S. Cheu, Veterans Administration Hospital, Fresno.

hyphae, mycelia and arthrospores which in turn are inhaled into the lungs of the host. Dust storms usually precede by roughly 10 to 20 days an outbreak of the disease.

Natural Course of the Disease[45]

Figure 3 depicts the natural course of coccidioidal infection. Half or more of primary infections do not produce symptoms. When symptoms are present, they may resemble those of influenza or pneumonia. Pulmonary residuals are the coccidioidoma, bronchiectasis, fibrosis, cavitation and calcification. The secondary or disseminated type may lead to death from acute meningitis or an overwhelming infection, or the patient may live for years with any system or systems involved. The meningitis eventually is fatal.

Symptoms of the Primary Disease[42, 46-48]

More than 40 per cent of persons who have primary coccidioidomycosis are without symptoms of the disease (figure 4). The outstanding symptoms resemble those of influenza. In cases in which cough is present, the spherule is found in the sputum in about 50 per cent of the cases when a diligent search is made. Eight per cent of the patients have arthralgia.

In an endemic area, the presence of erythema nodosum or erythema multiforme is almost pathognomonic of coccidioidal infection. In the differential diagnosis of erythema nodosum one must consider tuberculosis, drug reactions and rheumatic fever. These nonspecific cutaneous lesions occur in about 5 per cent of all primary coccidioidal infections and in about 20 per cent of the symptomatic cases. The incidence of the lesions is higher among female patients with symptomatic coccidioidal infection (about 40 per cent). Erythema nodosum usually is considered a good prognostic sign, but dissemination of the disease has been reported in cases in which it was present.[34, 49] Normally about one of every 200 cases of primary coccidioidomycosis progresses to the disseminated type of the disease,[50] whereas the rate when erythema nodosum is present is one in 700.

Erythema multiforme most commonly involves the upper half of the body, and ery-

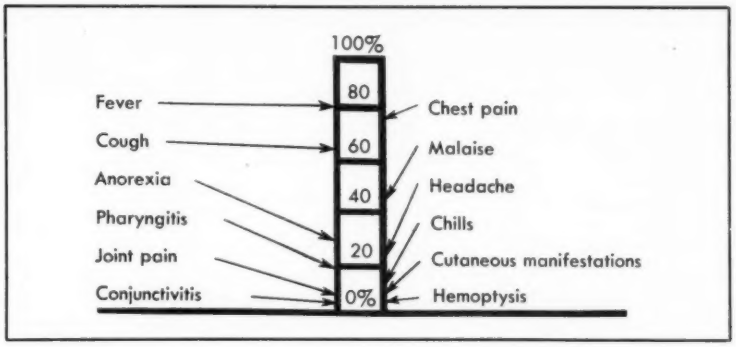

FIGURE 4. Symptoms of primary coccidioidomycosis. About half of primary infections are asymptomatic.

Figure 4 and the data in tables 1 through 5 were compiled with the assistance of George Paulsen, Bakersfield.

thema nodosum the lower half. The nodules of erythema nodosum are red initially and then fade to a purplish hue. The rash of erythema multiforme usually is discrete, erythematous and maculopapular. It often covers the entire trunk and upper extremities. Sometimes it looks like the rash of measles and sometimes it resembles urticaria. The erythema multiforme is a toxic rash and the erythema nodosum is a sensitivity rash; some workers believe they are the same.[51] They may be precipitated by skin testing with coccidioidin, and therefore when these rashes are present one should dilute the test material to a ratio of 1 to 1000 rather than using the usual strength of 1 to 100. Arthritis is another allergic manifestation.

Roentgenograms of the chest[34,52-56]—Roentgenographic evidence of primary coccidioidomycosis is present in as many as 85 per cent of the clinically recognized cases (table 1). Hilar lymphadenopathy, confluent consolidations, pleural effusions and peribronchial infiltrations are the common findings. Fibrosis, calcification and bronchiectasis may be residuals of the primary type of the disease. Pericarditis may occur in either the primary or the disseminated type.[57] The association of pulmonary coccidioidomycosis with pulmonary tuberculosis has been well documented in the literature.[58-69]

The most characteristic finding in a roentgenogram of the chest is a well-isolated, well-circumscribed nodular lesion (or, sometimes, multiple lesions) in the parenchyma of the lung, the coccidioidoma. It is benign in character, and after a period of months it resolves, develops into a cavitation, or persists as a solid lesion. If there is bronchial blockage, coccidioidomas may reappear. They may disappear or shrink to small fibrous nodules which subsequently may calcify or disappear. Large cavities may persist for years.

Complications of primary coccidioidomycosis are due principally to the residual pulmonary cavitations. If there is hemoptysis or infection, the cavitations may be removed surgically. If a cavity is less than 4 cm. in diameter and not peripherally located, it may be collapsed by means of pneumoperitoneum.[70] A peripherally situated cavity may cause a pneumothorax with or without empyema.

Manifestations of Secondary or Disseminated Coccidioidomycosis[19,42,71,72]

Because of their multiplicity, the symptoms of the secondary type of coccidioidomycosis are best grouped systemically (table 2). In coccidioidomycosis which progresses to the secondary type, the dissemination occurs in one to four months; the occurrence of dissemination years later is very unusual.

Men are about four times more susceptible to the disseminated disease than are women. In Kern County, California, 40 per cent of the disseminated cases occur among Caucasians, who comprise 87 per cent of the population, whereas nonwhite persons, comprising 13 per cent of the population, account for 59 per cent of the cases. Compared with the incidence among Caucasians, the incidence

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TABLE 1

PULMONARY MANIFESTATIONS OF PRIMARY COCCIDIOIDOMYCOSIS

Hilar lymphadenopathy
Pneumonic infiltration
Pleural effusion
Coccidioidoma
Chronic cavitation
Cystic cavity
Pneumothorax (peripheral cavity)
Bronchopleural fistula with empyema
Bronchiectasis
Pericarditis

TABLE 2

SYMPTOMS OF SECONDARY OR DISSEMINATED COCCIDIOIDOMYCOSIS

I. Symptomatic
A. Toxemic
B. Depending on system involved
1. Central nervous system (meningitic)
2. Bones and joints (osteolytic)
3. Skin (verrucoid granuloma)
4. Subcutaneous (indolent ulcer, draining abscesses)
5. Lymphatic (enlarged nodes and spleen)
6. Other systems
a. Pericarditis, myocarditis, endocarditis
b. Adrenal insufficiency
c. Peritonitis
d. Prostatitis
e. Epididymitis
C. Localized (chronic granulomas, hand and wrist, foot and ankle)
II. Asymptomatic
Serologic dissemination only

among Mexicans is 3.5 times greater, the incidence among Negroes is 14 times greater, and the incidence among Filipinos is 180 times greater. The death rate from coccidioidomycosis per 100,000 population (again compared with the death rate for white persons) is five times greater for Mexicans, 23 times greater for Negroes, and 192 times greater for Filipinos. Among white men, the rate of dissemination is approximately 1 per cent for those in whom the primary disease is diagnosed and 0.25 per cent for those who are infected. The incidence of dissemination for white women is one-fifth that reported for white men.

The average number of deaths from disseminated coccidioidomycosis reported annually for the entire United States is only 71.[73] In Kern County, an area of high incidence, the total deaths from coccidioidomycosis in the first 37 years in which the disease was reported (1901 to 1938) numbered less than the deaths from tuberculosis in any one year.[71]

Meningitis—Meningitis is the most significant lesion of disseminated coccidioidomycosis, and its onset may be insidious. The leptomeninges are involved. Spinal fluid pressure may exceed 600 mm. of water. Cellular increases of 500 to several thousand occur; polymorphonuclear leukocytes predominate at first, and, later, lymphocytes. There may be eosinophilia. Protein content may be increased to several hundred milligrams per cent. There may be a paretic gold pattern. Sugar content is reduced. Occasionally, culture of the spinal fluid will yield positive findings. The complement-fixation titer of the fluid may be elevated. Experimental drugs which have appeared to be beneficial in combating other manifestations of disseminated coccidioidomycosis have not altered the course of the meningitis; amphotericin B may prove to be the exception.[74] Involvement of the leptomeninges may lead to complete block of the spinal canal, with typical findings on examination of the spinal fluid.

Cutaneous manifestations—The most characteristic type of cutaneous lesion is the verrucoid granuloma, which is similar to that seen in blastomycosis. This lesion was present in the first case reported in the world and in the first case reported in the United States in 1896. In acute miliary dissemination, the granulomas appear in crops. A single lesion may be present in a milder case of the disseminated disease. The verrucoid granuloma often appears first on the face or scalp, but it may appear anywhere. A characteristic site is the nasolabial fold. A single lesion may be the only sign of dissemination.

Subcutaneous abscesses—One of the most common cutaneous lesions in chronic coccidioidomycosis is the indolent ulcer, which represents a sinus tract originating in the sub-

cutaneous tissue, bone or viscera. It is frequently seen over the joints of the foot and ankle and of the hand and wrist. Secondary bacterial infection of the intervening skin produces a granulomatous mass that is foul and angry-looking.

Involvement of lymph nodes—The lymph nodes on the surface of the body are involved extensively, particularly the thoracic hilar nodes. Differentiation from the lymphomas may be difficult. In the community in which I live, an occasional case of coexisting Hodgkin's disease and disseminated coccidioidomycosis has been seen.[75]

Spleen and liver—Involvement of the spleen may be secondary to an acute splenic tumor and specific mycotic granulomas of the miliary type. Hepatic enlargement may be secondary to general toxicity and miliary granulomas, abscesses, or both.

Arthritis—Coccidioidal arthritis closely resembles tuberculous arthritis. Arthritis has been noted in about one-third of the chronic disseminated cases.

Osteomyelitis—Osteomyelitis occurs in many of the disseminated cases. Only cutaneous lesions are more characteristic. The bones most commonly involved are the ribs, vertebrae, skull and bones of the extremities. The osteomyelitis is primarily an osteolytic process with a later tendency to strong osteoblastic activity, sometimes with complete healing. Although the skull and vertebrae may be involved extensively, meningitis is rarely secondary to this involvement.

Genitourinary system—Pregnancy perhaps aggravates the dissemination of coccidioidomycosis, especially in the third trimester.[76-78] The placenta is a barrier to transmission of the spherule to the fetus, but it does not prevent the complement-fixing antibody from crossing into the fetal blood stream.[79-81]

In about 50 per cent of fatal cases of disseminated coccidioidomycosis, there is microscopic evidence of renal involvement with miliary granulomas or abscesses; these usually are not grossly visible. Adrenal insufficiency has been noted only rarely from extensive adrenal involvement.[82,83]

Gastrointestinal tract—The disseminated type of coccidioidomycosis, unlike tuberculosis, spares the gastrointestinal tract.

Pathology[19,31-33,42]

Gross—The mildest pulmonary lesions are like any bacterial pneumonia; little fibrin is present, so resolution can take place. In more severe disease, the lesions are such that healing can occur only by hyalinization and fibrosis. There may be bronchitis, bronchiolitis and bronchiectasis. Hilar and mediastinal lymph nodes are enlarged and contain the characteristic granulomatous lesions.

Microscopic—The microscopic changes are not unlike those in tuberculosis. In the lungs an exudative reaction may take place which resolves completely without residuals. In more severe disease there is a balance between the mature granulomatous and the suppurative reactions. Primary pulmonary lesions are predominantly granulomatous, and disseminated pulmonary lesions are predominantly suppurative in character.

In the suppurative phase, polymorphonuclear reaction takes place when endospores are liberated from the mature sporangium or spherule. There is an attempt by the polymorphonuclear cells to phagocytize the spores. Bloody fluid escapes, with widespread necrosis and liquefaction.

In the granulomatous phase, large mononuclear cells appear when the endospore has become a spherule. They attempt to digest the invading organism. There is at this time proliferation of the host's tissues. Epithelioid cells coalesce to form giant cells. Usually there are many nuclei arranged radially in a rosette about the periphery—the Langhans giant cell. Sometimes nuclei are scattered haphazardly throughout the cytoplasm—the foreign-body giant cell. When caseation or coagulation necrosis occurs, epithelioid cells lose their outline, and nuclei disappear and their structure fades. Around the epithelioid and giant cells a zone of lymphocytes and plasma cells appears—the tubercle with a homogenous necrotic center. The stained spherule or sporangium establishes the specific diagnosis.

Staining methods—Hematoxylin and eosin will demonstrate *C. immitis*, but is not com-

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TABLE 3

LABORATORY AIDS TO DIAGNOSIS OF COCCIDIOIDOMYCOSIS

PROCEDURE	REACTION TO TEST		
	Acute benign	*Acute severe focal (not disseminated)*	*Disseminated*
Skin test	Positive	Positive	Negative
Precipitin titer	Negative (or positive)	Positive	Negative (or positive)
Complement fixation	Negative	Negative (or positive)	Positive

pletely satisfactory. The periodic acid-Schiff (PAS) technic (Hotchkiss-McManus modification) is superior.[84] Gridley[85] has modified this technic so that hyphae stain deep blue and spherules deep rose or purple against a bright yellow background.

Laboratory Aids to Diagnosis

The presence of *C. immitis* in the body evokes a rapid and usually effective immunologic response on the part of the host.[81,86] Immunity is considered to be lifelong and complete. Second attacks of coccidioidomycosis probably do not occur naturally, although reinfections have been reported from massive exposures.[87]

There are three tests which use coccidioidin, the filtrate of the cultures of many strains of *C. immitis*, as the antigen. They are the coccidioidin skin test, the precipitin test, and the complement-fixation test performed by the Smith technic.

Skin test—The coccidioidin skin test is performed in the same way as the tuberculin skin test. A maximal response occurs from 2 to 21 days after the first symptoms or 9 to 42 days after exposure to *C. immitis*. A positive skin reaction to coccidioidin usually persists as positive on subsequent testing. The result of the skin test is most significant when a negative response is converted to a positive one. The reaction to the skin test becomes positive during the first week of the acute illness in more than 80 per cent of the cases, and by the end of the second week in more than 90 per cent. By the end of the third week the reaction is positive in approximately 100 per cent of cases.

Early in the primary disease, the reaction to the coccidioidin skin test is negative, and a negative reaction also occurs in many of the disseminated cases.

The needles and syringe used for testing must never have been used for any other biologic preparation, notably blastomycin, histoplasmin or tuberculin. An induration 5 mm. in diameter, with erythema,[81] in 24 to 48 hours is diagnostically significant. Histoplasmosis, halo sporangium and blastomycosis may give cross reactions.[81]

Precipitin test—Precipitins form after skin sensitization. They appear in about 50 per cent of symptomatic cases of coccidioidomycosis during the first week, in 85 per cent by the end of the second week, and in about 90 per cent by the end of the third week. By the fourth week, precipitins begin to disappear, so that there are few positive reactors to the precipitin test after about 12 to 16 weeks. Once they have disappeared, they usually reappear only when a residual pulmonary cavity ruptures, with empyema. A positive reaction with any dilution is diagnostic of the acute disease. The precipitin test requires five days to complete.

Complement-fixation test—The complement-fixation test used for coccidioidomycosis is like the Kolmer test but has been modified by Smith. The complement antibodies develop more slowly than precipitins. About 10 per cent of persons with coccidioidal infection are positive reactors in the first week. Complement antibodies continue to appear for 12 weeks, whereas new precipitins rarely appear after the first month. The complement-fixation titer may be at a low level for months. An

TABLE 4

LABORATORY FINDINGS IN COCCIDIOIDOMYCOSIS

	PRIMARY	DISSEMINATED
Hematology		
Leukocytosis	+	+
Later, lymphocytosis	+	
Eosinophilia	+	+
Elevated sedimentation rate	+	+
Mycology		
Wet mount	+	+
Stained section	+	+
Culture	+	+
Animal inoculation	+	+
Immunology		
Skin test	+	+−
Precipitin test	+−	−
Complement fixation	−	+

TABLE 5

SURGICAL INDICATIONS IN FOCALIZED PULMONARY COCCIDIOIDOMYCOSIS

URGENT

1. Enlarging or tension cavity
2. Ruptured cavity
   a. Bronchopleural fistula
   b. Empyema

ELECTIVE

1. Chronic lung abscess (six months or more)
2. Hemoptysis (repeated minimal or gross)
3. Residual indication after acute infection
   a. Coccidioidoma versus malignancy
   b. "Corseted" lung
   c. Bronchiectasis

The tables presented here were prepared with the assistance of George Paulsen, Bakersfield, California.

occasional case of histoplasmosis with a strongly positive reaction to the histoplasmosis complement-fixation test will yield a weakly positive coccidioidal complement-fixation test response. Blastomycin may give complement-fixation titers in coccidioidomycosis. Serologic tests for syphilis may yield false positive results in disseminated coccidioidomycosis. In the latter type of the disease the titer usually is persistently positive in the higher dilutions; there are some asymptomatic cases with such titers in which it is thought that latent foci of the active disease are present, but this has not been proved. Interpretation of the complement-fixation test must be correlated with the clinical findings.

As shown in table 3, in the primary acute benign disease the skin test yields a positive result and the complement-fixation and precipitin tests usually give negative results. In the primary acute severe case, results of the skin and the precipitin tests are positive and the complement-fixation test result may be positive, usually for short periods (6 to 12 months) and usually in the lower dilutions. In the presence of benign residual pulmonary lesions the complement-fixation titer may persist at a low level for several years. In the disseminated type of coccidioidomycosis the skin and precipitin tests usually give negative results, and the complement-fixation titer usually is persistently positive in the higher dilutions. However, there may be chronic coccidioidal meningitis of long duration with low-titer complement fixation.[42]

Hematologic findings—Leukocytosis is present in both the primary and the disseminated types (table 4). In the healing stage, lymphocytosis is observed. In an endemic area, eosinophilia strongly suggests the possibility of the primary disease. The sedimentation rate is elevated in both types.

Mycologic findings—Wet mounts, stained sections, cultures and animal inoculations are important in the diagnosis of coccidioidomycosis. Material from sputum, draining abscesses and bronchial aspirate can be used for any of these tests. The spherule or sporangium must be seen, or positive cultures obtained, to establish the diagnosis. Closed culture tubes are preferable to Petri dishes, which are dangerous because they may cause laboratory infections.

Indications for Thoracic Surgical Procedures[88-90]

The indications for urgent surgical intervention and for elective surgical procedures in focalized pulmonary coccidioidomycosis are given in table 5. An enlarging cavity and rupture of a cavity are indications for urgent surgical treatment. Elective operative treatment is indicated by the presence of a chronic pulmonary abscess for six months or

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longer, the occurrence of hemoptysis, and residual effects of acute infection.

Medical Therapy

In the medical treatment of disseminated coccidioidomycosis, more than 50 substances have been tried. None have been consistently successful. Amphotericin B is showing some promise,[74] but because of renal toxicity (tubular necrosis), hemolysis and side effects it leaves much to be desired. It appears to be the best drug we have at the present time for treatment of disseminated coccidioidomycosis.

The references listed here are presented as a guide to the literature on coccidioidomycosis. The references cited in the text will be included in the author's reprints; copies of the references may be obtained from the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

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BOOKS RECEIVED

Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Reviews in this issue start on page A-161; additional listings appear on page 338.

Roentgenology of Intracranial Meningiomas. By Sidney P. Traub, M.D., Associate Professor of Radiology, University of Saskatchewan College of Medicine, Saskatoon. 238 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $14.00.

Internal Medicine: Current Journal Review. Medical Examination Review Book. Vol. 7. 194 pages. 1961, Medical Examination Publishing Company Inc., Flushing, New York. $6.00.

Introduction to the Clinical Laboratory. By Robert P. MacFate, Ph.D., Chief, Division of Laboratories, Board of Health, Chicago. 448 pages with 80 illustrations. 1961, Year Book Medical Publishers, Inc., Chicago. $10.00.

Illustrations of the Nervous System. By Louis Hausman, M.D., Professor of Clinical Medicine (Neurology), Emeritus, Cornell University Medical College, New York. Atlas III. 168 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $9.50.

Recurrent Dislocation of the Shoulder. By H. F. Moseley, F.R.C.S., Associate Professor of Surgery, McGill University Faculty of Medicine, Montreal, Quebec. 163 pages with 83 illustrations, 10 color plates, and 35 stereoscopic color photographs. 1961, McGill University Press, Montreal. $13.50.

Essentials of Neurosurgery; for Students and Practitioners. By Sean Mullan, M.D., Associate Professor of Neurosurgery, University of Chicago School of Medicine, Chicago. 273 pages with 87 illustrations. 1961, Springer Publishing Company, Inc., New York. $6.75.

Annals of the New York Academy of Sciences, 1961. Genetic Perspectives in Disease Resistance and Susceptibility. Vol. 91, Art. 3. 223 pages, illustrated.

Selected Readings in Pathology. By Esmond R. Long, M.D., Professor Emeritus of Pathology, Henry Phipps Institute, University of Pennsylvania School of Medicine, Philadelphia. Ed. 2. 306 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $8.50.

A Synopsis of Physiology (Rendle Short). Edited by C. C. N. Vass, Ph.D., Reader in Physiology, University of London Faculty of Medicine, London, England. Ed. 5. 348 pages, illustrated. 1961, The Williams & Wilkins Company, Baltimore. $8.00.

The Merck Manual of Diagnosis and Therapy. Edited by Charles E. Lyght, M.D., Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey. Ed. 10. 1,907 pages with 45 illustrations. 1961, Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey. Regular edition, $7.50; de luxe edition, $9.75.

A Handbook of Emotional Illness and Treatment. By Richard C. Robertiello, M.D., Chief Psychiatrist, Long Island Consultation Center, New York. 159 pages. 1961, Argonaut Books, Inc., Larchmont, New York. Distributed by The Citadel Press, New York. $3.95.

Primaquine-Sensitive Type of Drug-Induced Hemolytic Anemia

WILLIAM H. ZINKHAM*

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The hemolytic effects of certain drugs and chemicals have been related to an inborn error of red blood cell metabolism. Persons with this defect are normal until exposed to moderate doses of certain compounds, of which primaquine is a notable example. The erythrocytic defect has been observed in many ethnic groups, the incidence of abnormality varying from 2 to 25 per cent. Clinical manifestations of drug-induced hemolysis vary according to the agent ingested. The author discusses the diagnosis, treatment and importance of this phenomenon, and points out that it will become increasingly significant.

WILLIAM H. ZINKHAM

THE administration of certain drugs and chemicals may be associated with the development of a hemolytic anemia. In some individuals the degree of hemolysis is so mild that its presence escapes detection; in others, the anemia is quite severe, and blood transfusions are sometimes necessary to maintain life. The list of compounds with this hemolytic capacity encompasses a variety of substances, from the simple inorganic metals, such as lead and arsenic, to the complex organic chemicals listed in modern drug encyclopedias.

Although the manner in which these agents evoke hemolysis has not been defined, clinical observations indicate that most of these substances can be placed in one of two groups. In the first group are those compounds which regularly hemolyze the red blood cells of anyone to whom they are given; the second group consists of agents which induce a hemolytic response in certain susceptible individuals. The classic representative of the first group is phenylhydrazine, a chemical which can effect hemolysis in both man and animals. In most individuals the severity of the anemia is related to the amount of phenylhydrazine administered, and it is this dose-effect relation that led to the use of this chemical in the treatment of patients who have polycythemia vera.[1]

Primaquine, naphthalene and sulfanilamide

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TABLE 1

BIOCHEMICAL ABNORMALITIES* OF PRIMAQUINE-SENSITIVE RED BLOOD CELLS

Low reduced glutathione
Instability of glutathione
Deficiency of glucose 6-phosphate dehydrogenase activity
Decreased activity of catalase
Decrease of total lipids of the red blood cells during hemolysis
Increased activity of aldolase and glutathione reductase

*Alving and co-workers[3] have listed specific references to each of these abnormalities.

TABLE 2

COMPOUNDS WHICH HAVE INDUCED A HEMOLYTIC ANEMIA IN PERSONS WITH PRIMAQUINE-SENSITIVE ERYTHROCYTES

Primaquine	FURADANTIN®
Sulfanilamide	GANTRISIN®
Acetanilid	KYNEX®
Sulfoxone sodium	AZULFIDINE®
Phenacetin	Naphthalene
Para-aminosalicylic acid	Vitamin K (water-soluble analogue)
Probenecid	Aspirin
PYRAMIDON®	
Thiazolsulfone	

are examples of the second group of hemolytic compounds. These chemicals, in therapeutic amounts, effect an acute hemolytic reaction in only a few of the persons to whom they are administered. Numerous hypotheses have been proposed to explain this susceptibility; only recently, however, has it been demonstrated that sensitivity to hemolysis is related to an intrinsic defect of the red cell.

The Primaquine-Sensitive Red Cell

Prior to and during World War II, a large number of compounds were screened for their antimalarial activity. One of these was primaquine, a derivative of 8-aminoquinoline. When this compound was administered to 100 Negro men, acute intravascular hemolysis developed in about 10. A similar dose of primaquine rarely hemolyzed the red cells of Caucasian men. Alving, Beutler, Carson, Dern and others at the University of Chicago followed up these initial observations with a series of in vivo and in vitro experiments to determine the mechanism of primaquine-induced hemolysis. Their results constitute one of the high lights of modern clinical research and, as was to be expected, have stimulated the interests and activities of many other investigators.

In brief, Alving and co-workers first showed that primaquine sensitivity was due to some intrinsic defect of the red cell. Unlike abnormalities of the erythrocyte previously described, this defect could not be defined by routine morphologic or immunologic technics. It was further shown that the hemolytic process was self-limited, and that hemolysis affected primarily the older erythrocytes. The first clear-cut in vitro definition of primaquine-sensitive erythrocytes was devised by Beutler, who showed that these cells have a greater propensity than do normal red cells to develop toxic granules, Heinz bodies, when incubated with a variety of chemicals.

A list of the biochemical deviations demonstrated to date in primaquine-sensitive cells is shown in table 1. Several of these metabolic properties may be used for the in vitro detection of drug-sensitive erythrocytes, and their application in this regard will be discussed later. Still unsolved is the relation between these abnormalities and the factors which limit the survival time of red cells exposed to hemolytic agents. The past, present and future of primaquine sensitivity have been reviewed by several of the investigators who originally contributed to its elucidation.[2-4]

Clinical Aspects of Drug-Induced Hemolysis

The primaquine-sensitive type of hemolysis has become a model for the study of other drug-induced hemolytic anemias, and it is now apparent that the selective hemolytic activity of many compounds can be related to the erythrocytic defect of primaquine sensitivity. A partial listing of drugs which may hemolyze the red cells of primaquine-sensitive individuals is shown in table 2. With therapeutic

doses of these compounds, the degree of hemolysis ranges from slight (as with aspirin) to quite severe (as with the naphthalene derivatives).

The hemolytic capacity of various compounds given to primaquine-sensitive adults has been studied by Kellermeyer and coworkers[5] under carefully controlled conditions. Aspirin, in a daily dosage of 4 gm. by mouth, reduced the survival of chromium^{51}-labeled red cells to two-thirds of normal. Although greater hemolysis was observed when the daily dosage was increased to 12 gm., the reduction in the hematocrit reading never exceeded 8 mm. The shortening in the survival time of primaquine-sensitive red cells and the concomitant anemia were more marked following the oral administration of AZULFIDINE®. Daily dosages of 4, 6 and 8 gm. decreased the life span of the erythrocytes to approximately two-thirds, one-fourth and one-eighth of normal, respectively. Maximal reticulocyte counts varied from 6 per cent with the lowest to 13 per cent with the highest dosage. Red cell survival studies have not been done with naphthalene or its derivatives. Clinical observations, however, suggest that the life span of the red cell is even shorter than that seen with the compounds mentioned before.

Obviously, the clinical manifestations of drug-induced hemolysis will vary according to the drug or chemical ingested. Irritability, abdominal and back pain, pallor, red urine, and scleral icterus constitute the clinical events which are to be expected in the primaquine-sensitive person who is exposed to naphthalene. All these symptoms usually appear within a period of 72 hours after contact with naphthalene. The clinical symptoms of the hemolytic anemia secondary to administration of aspirin, FURADANTIN®, GANTRISIN® or KYNEX® are milder, and the first indication of hemolysis may be a moderate decrease in the hematocrit reading.

The self-limited nature of the process also masks the occurrence of drug-induced hemolysis. Dern, Beutler and Alving[6] have shown that the acute hemolytic phase following the administration of primaquine lasts about one week, after which time clinical symptoms disappear, the urine clears, and the peripheral blood returns to normal, even though the drug is continued. A similar state of refractoriness also has been observed with some of the other hemolytic compounds.

Diagnosis of Drug-Induced Hemolysis

The essential ingredients for diagnosing the primaquine-sensitive type of hemolysis are (1) historical or chemical evidence of exposure to a hemolytic agent, (2) laboratory data indicative of drug-induced hemolysis, and (3) demonstration of the erythrocytic defect of primaquine sensitivity.

Familiarity with the list of compounds capable of hemolyzing primaquine-sensitive red cells will enable the clinician to elicit a positive history of contact with these agents. Naphthalene, for example, is such a common household item that a mother usually does not consider it relevant that her child sucked on a moth ball several days prior to the appearance of red urine and pallor. Unless the clinician were cognizant of the hemolytic effects of naphthalene, its etiologic role would be ignored. Equally important is a knowledge of the various forms in which these hemolytic agents might exist in the patient's environment. Hemoglobinuria developed in a Negro boy two days after he nibbled on a cake of deodorant suspended above the living room mantle. Chemical analysis revealed that over 95 per cent of the material was naphthalene. Phenacetin, another compound deleterious to primaquine-sensitive red cells, is a constituent of many galenic preparations for the relief of headaches, colds and fever. The drug-sensitive person with fever who ingests tablets containing phenacetin may become anemic. Sometimes this anemia can be related to the underlying illness; another cause, however, is the occurrence of hemolysis after exposure to phenacetin.

Many of the changes noted in the peripheral blood of patients with drug-induced hemolysis are similar to those observed in other types of hemolytic anemia, namely, a falling hematocrit reading, an elevated reticulocyte count, and an increased amount of urobilin in the stool. When the hemolytic process is more ex-

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plosive, hemoglobinemia and hemoglobinuria may occur, followed by hyperbilirubinemia and methemalbuminemia. Certain abnormalities of the erythrocyte have been described which are pathognomonic of drug-induced hemolysis. One of these is the striking alteration of red cell morphology first reported by Zeulzer and Apt[7] in naphthalene-induced anemia. Many of the red cells are microspherocytes, and some show a marked distortion of shape. Instead of a smooth, round contour, the cells have jagged edges; in a few, the hemoglobin is concentrated to one side, and a clear membrane is seen on the other side. Gasser[8] described similar morphologic changes in the blood of prematures receiving excessive dosages of a water-soluble analogue of vitamin K, a compound with a structure similar to that of the naphthalene metabolites. The term "egg-shell forms" was used to describe the fragmentation of the red cells occurring in these babies. Only slight variations of red cell morphology are seen in patients with mild anemia after exposure to drugs.

Another significant alteration of the blood sometimes seen in drug-induced hemolysis is the appearance of Heinz bodies in the red cells. Morphologically, Heinz bodies are round or serrated refractile bodies which can be demonstrated by adding supravital stains to wet preparations of blood. They are not visible when blood smears are stained by Wright's technic. Heinz bodies usually appear in the older red cells, and, since these cells are the ones first removed from the circulation, they are seen in the peripheral blood only in the early phases of drug-induced hemolysis. Although many chemicals may produce Heinz bodies in the erythrocyte, only a few have been shown to have this effect in the primaquine-sensitive type of hemolysis, e.g., primaquine and naphthalene. Severe hemolysis also has been observed in primaquine-sensitive individuals after the ingestion of beans of *Vicia fava,* a vegetable which is a dietary staple in the Mediterranean littoral. As with naphthalene, the hemolytic anemia may be quite explosive, and marked aberrations of red cell morphology and Heinz-body formation have been reported.[9] Perhaps these latter changes are an indication of the severity of the hemolytic process.

The *sine qua non* for diagnosing the primaquine-sensitive type of hemolysis is a demonstration of the primaquine-sensitive defect in the patient's erythrocytes. Several in vitro technics are currently available to distinguish erythrocytes of drug-sensitive persons from those of normal individuals. The first of these is a quantitative evaluation of Heinz-body formation in red cells exposed to acetylphenylhydrazine. A greater number of Heinz bodies are formed in drug-sensitive red cells. Although the test is easily performed, false positive results may occur unless the experimental conditions are carefully controlled. The second method is the glutathione stability test which was devised by Beutler.[2] Glutathione levels are measured in whole blood before and after its exposure to acetylphenylhydrazine. In the nonsensitive person, there is only a slight reduction in the concentration of glutathione, whereas in the drug-sensitive individual there is a marked drop. The third method is a direct assay of the enzyme glucose 6-phosphate dehydrogenase, which is deficient in primaquine-sensitive red cells. Although this technic would be difficult to carry out in routine diagnostic laboratories, it is the only method available which provides a precise quantification of enzyme activity. Motulsky has recently described a simple screening test for detecting drug-sensitive red cells which consists of adding brilliant cresyl blue to hemolysate containing the reactants of the enzyme glucose 6-phosphate dehydrogenase. In the normal person, the dye is decolorized in one hour; in the primaquine-sensitive hemolysate, the color is unchanged.[10]

Glutathione and enzyme values may become normal when the primaquine-sensitive patient is undergoing a hemolytic crisis. In this situation one can either wait until the peripheral blood findings return to normal or study the erythrocytes of available family members. It has been established that the primaquine-sensitive characteristic is genetically determined and is transmitted by a sex-linked gene of intermediate dominance. If a boy has the defect in his red cells, his mother should have

a partial or complete expression of the characteristic in her blood. If the defect is found in a girl, the mother may have a partial or a complete deficiency of the enzyme, while the father must manifest the complete defect. Studies on the red cells from the progeny of the primaquine-sensitive patients also may be helpful. All the sons of a primaquine-sensitive mother should manifest the abnormality in their erythrocytes, and all the daughters of a drug-sensitive father should show a partial deficiency.

Therapy of Drug-Induced Hemolysis

The majority of drug-sensitive persons are never aware of the abnormality in their erythrocytes, and, since the defect cannot be defined by standard hematologic technics, it is highly probable that none of them will ever learn of its existence. When a patient with the primaquine-sensitive type of hemolysis is observed in this clinic, other members of the family are studied. Those individuals found to have a similar defect are advised of its presence and are told that certain drugs or chemicals may be harmful to their blood. Each is given a list of the compounds known to hemolyze primaquine-sensitive red cells.

The anemia occurring after exposure to naphthalene and naphthalenelike compounds may be so severe that blood transfusions are sometimes lifesaving. Since many of these patients have residual amounts of the hemolytic substance in their circulation at the time of the transfusion, the administration of blood from a sensitive donor may result in a hemolytic transfusion reaction. Although transfusion reactions of this nature have not been reported, the safest procedure would be to transfuse with blood from a nonsensitive donor.

Clinical Importance of Primaquine Sensitivity

The genetic predisposition to the primaquine-sensitive type of hemolysis has a worldwide distribution. The defect has been observed in the red cells of many ethnic groups, including American Negroes, Asiatic Indians, Greeks, Italians and Sephardic Jews, and the incidence of the abnormality varies from 2 to 25 per cent. In American Negroes, for example, 2 per cent of the females and 14 per cent of the males are affected. Furthermore, the list of substances capable of hemolyzing drug-sensitive red cells is constantly growing, and it can be assumed that the hemolytic potential of other compounds will eventually be documented. One must conclude, therefore, that drug-induced hemolysis will continue to occur, and, as the occurrence of this entity is more frequently recognized by physicians, that its clinical significance will undoubtedly increase.

The importance of recognizing the hemolytic potential of drugs has recently been emphasized in the care of newborn babies. A common practice in many nurseries is the administration of vitamin K compounds to prevent the occurrence of hemorrhagic disease of the newborn. Several years ago, the English noted a high incidence of hyperbilirubinemia and associated kernicterus in premature who had received 30 to 50 mg. of SYNKAYVITE®, a water-soluble analogue of vitamin K.[11] Before this experience, Gasser[8] had described the occurrence of spontaneous Heinz-body anemia in prematures who were given similar amounts of the same compound. The characteristics of this anemia were similar to those seen in patients hemolyzing after exposure to naphthalene. It has since been pointed out that the vitamin K analogues are structurally related to the metabolites of naphthalene, and on the basis of this structural similarity it could have been predicted that some of the vitamin K compounds would be deleterious to the red cell.

Although large doses of Synkayvite were necessary to hemolyze the erythrocytes of nonsensitive prematures, the question arose as to what amount could safely be administered to the primaquine-sensitive newborn. For example, a severe hemolytic anemia developed in one full-term Negro male infant after he received 10 mg. of another water-soluble K analogue, HYKINONE®. While the in vitro effects of these and other vitamin K compounds on glutathione metabolism of primaquine-sensitive erythrocytes were being studied, it

was determined that as little as 0.01 mg. of Hykinone and 0.025 mg. of Synkayvite added to 1.0 ml. of blood resulted in a marked reduction of glutathione. Heinz-body formation also was observed. KONAKION®, a water-soluble preparation of vitamin K_1, did not show either effect, even when 1.0 mg. was added to the blood. On the basis of these observations, varying amounts of Synkayvite and Konakion were given to a series of normal newborns with primaquine-sensitive red cells. It has now been established that 2.5 mg. of Synkayvite and as much as 5.0 mg. of Konakion will not hemolyze the red cells of these babies. A dose of 1.0 mg. of either compound is sufficient to prevent the occurrence of hemorrhagic disease in the full-term baby.

Other clinical applications of the primaquine-sensitive phenomenon will undoubtedly be reported; as they are, the clinical importance of this interesting abnormality will eventually be recognized.

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Recognition of Congenital Abnormalities in Children

CARL C. FISCHER*

Hahnemann Medical College and Hospital, Philadelphia

A high index of suspicion based primarily on a careful family and maternal history, an understanding of the numerous causative factors, and keenness of observation are important in identifying congenital abnormalities, many of which can be detected only if one is searching for them. Specific tests for all the abnormalities are obviously impractical in the average case, but if the possibility of their presence is borne in mind they will more often be recognized and corrected at an early age.

CARL C. FISCHER

VARIOUS estimates have been made of the incidence of congenital abnormalities in newborn infants. A recent study of all infants born in 1957 in Belfast, Ireland, gave a rate of 14.1 per thousand births (120 infants with gross malformations among 8,519 pregnancies). Add to these gross malformations the many minor abnormalities detected later in life, and the figure undoubtedly approaches the 5 to 6 per cent some writers have suggested.

Congenital abnormalities account for a significant number of neonatal deaths. Of the neonatal deaths depicted graphically in figure 1, they were responsible for 1.8 deaths per thousand live births in the first week of life, with an additional rate of 0.7 per thousand from the seventh to the twenty-seventh day of life, for a total of 2.5 deaths per thousand live births. Stated another way, congenital malformations account for about one-fifth of the deaths in the first week of life and one-sixth in the first month. These figures have remained stubbornly similar through the years despite the marked lowering of the infant death rate through the conquering of infection, and thus congenital abnormalities merit our deepest concern.

Of primary importance is the recognition

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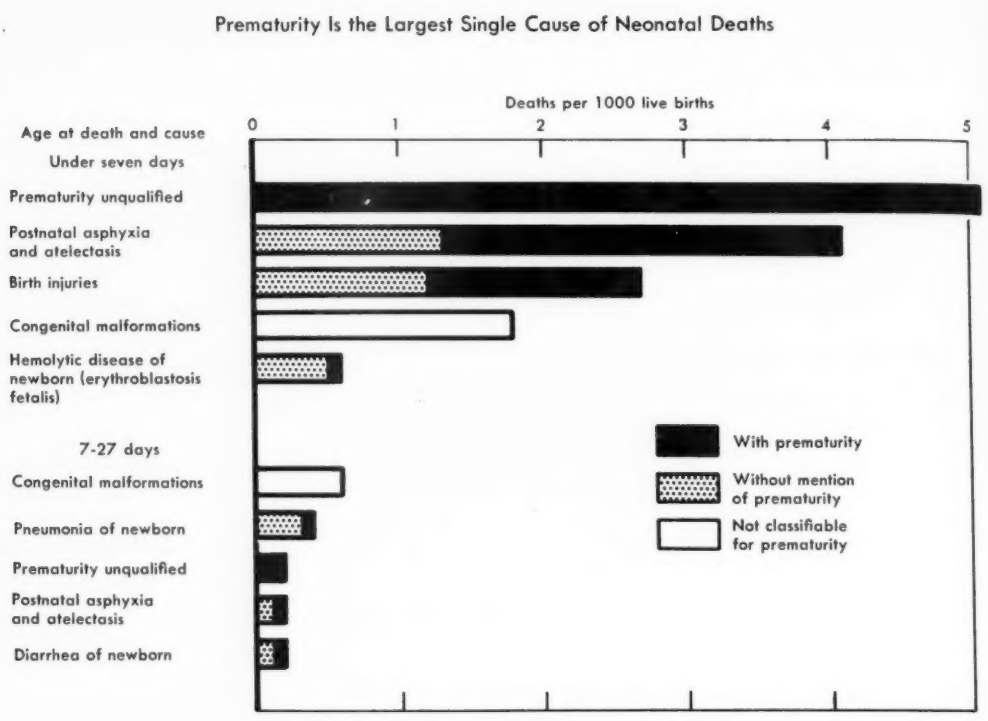

FIGURE 1. Causes of neonatal death in order of frequency.

of congenital abnormalities as soon after birth as possible. To do this, we must have a high index of suspicion, and this can be engendered only through a review and a continuing awareness of the numerous conditions during intrauterine life which may result in abnormalities in the fetus.

Specific Environmental Causes

Radiation—There is general awareness of the dangers of radiation during pregnancy, particularly in the early months. Considerable progress is being made in reducing this hazard, through elimination of unnecessary radiation procedures and through careful screening. Similar measures designed to protect the gonadal areas of all persons up through the childbearing age are also generally accepted. Many investigative groups are working on the problem of atomic radiation, and I will not attempt to discuss it here.

Infection—Viral—Of the viral infections, rubella or German measles has received the most attention, primarily because of the early and comprehensive work of Gregg in Australia. Other viral diseases such as mumps and infectious hepatitis have been similarly incriminated as etiologic factors in congenital abnormalities, particularly when the mother is infected in the first three months of pregnancy. It is extremely difficult to establish the exact role of these infections in the production of fetal abnormalities, because most studies are made after the infections have been detected and because many instances in which the mother has been infected and her offspring is normal are completely overlooked. However, figures indicating that 10 to 30 per cent of women who are infected with rubella during the first trimester of pregnancy will give birth to abnormal infants are sufficiently accepted to give serious cause for thought when this problem arises.

Bacterial—Bacterial infection may pass

from mother to fetus as a result of bacteremia (e.g., pneumococcal pneumonia), as a result of direct infection of the placenta (tuberculosis), or by direct contact in the maternal passages during labor (gonorrhea). Syphilis also may pass to the fetus by means of placental infection. Fortunately, the decrease in active syphilitic infections among pregnant women and early detection of the disease through prenatal blood testing have greatly reduced the incidence of congenital malformations due to syphilis. But complacency often follows improvement in the control of a disease, and recent reports suggest that venereal disease is on the upswing. We must not let down our guard against it.

Protozoan—We must think also of protozoan infections, particularly congenital toxoplasmosis, which produces signs of illness in the infant from the time of birth. Although relatively rare in most areas, this disease occurs comparatively frequently in certain regions and should always be kept in mind. Malaria in the offspring of a mother infected with this disease is also a possibility.

Deficiencies—Congenital abnormalities related to various deficiencies in the mother have been demonstrated most often in experimental animals. However, we have noted acute deficiency of folic acid in human infants as a result of administration of AMINOPTERIN® to the mother.

Drugs—Recent studies reveal a high percentage of abnormalities among infants born of women who receive certain hormones, e.g., PROGESTIN®. Cases are reported in which excessive estrogen therapy similarly seems to be an etiologic factor.

Specific Genetic Causes

Specific genetic causes of congenital abnormalities are too numerous to include here. The interested reader is referred to the excellent article by Dr. Frazier on "Medical genetics in pediatrics" in the January 1954 issue of the *Journal of Pediatrics*. Dr. Frazier listed 154 hereditary conditions believed to be of genetic origin and emphasized that the list was not complete. These conditions run the gamut from acatalasia to xeroderma pigmentosum.

Congenital Abnormalities Without Identifiable Specific Cause

Admittedly, there are many congenital abnormalities whose specific causes cannot be identified. Most of the abnormalities that we see result from complicated interaction between genetic predispositions and intrauterine environmental factors.

Recognition of Congenital Abnormalities

Signs and symptoms in the mother—It would seem of value to pay attention to the signs and symptoms in the mother which might lead one to suspect the possibility of a congenital abnormality even when the history is noncontributory. Chief among these signs is polyhydramnios, which in a majority of instances suggests multiple births, tracheoesophageal fistula with atresia, high intestinal obstruction, erythroblastosis fetalis, or anencephalia. Tracheoesophageal fistula can be ruled out readily by passing a soft rubber catheter into the stomach of the infant. Carefully made scout films of the abdomen in several positions a few hours after birth may reveal intestinal obstruction. Lloyd and Clatworthy in a review of 220 cases of upper intestinal obstruction found that polyhydramnios in the mother had been present in approximately one of every seven cases.

The reverse condition, oligohydramnios in the mother, frequently suggests gross renal abnormalities in the fetus such as agenesis or polycystic kidneys.

Recognition at the optimal time—Having established a background for a high index of suspicion, what can we do to recognize congenital abnormalities at the optimal time? Obviously, the first essential item is a careful examination of the infant at the time of birth followed by an even more detailed one shortly thereafter. The recently introduced method of judging the newborn infant's condition immediately after birth according to the Apgar scoring system (figure 2) gives a great deal of help in this direction. An Apgar rating of less than 7 strongly suggests the presence of a condition incompatible with survival unless

Apgar Scoring System

Sign	0	1	2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Reflex irritability	No response	Cry	Vigorous cry
Color	Blue, pale	Body pink, extremities blue	Completely pink

FIGURE 2. Apgar scoring system (after Dr. Virginia Apgar).

immediate steps are taken to combat it, and use of this method of judging the newborn infant should increase awareness of the possibility of congenital defects.

Recognition of defects which are not apparent even when a careful physical examination is made—Unfortunately there are a great many congenital defects which cannot be recognized even by a careful physical examination; I shall review these conditions briefly.

Central nervous system—It is obviously difficult to detect abnormalities of the central nervous system when they are not associated with gross defects of the skull or spine. Identification usually awaits the development of specific symptoms indicating malformation of

FIGURE 3. Spina bifida (rachischisis) of the lumbosacral region.

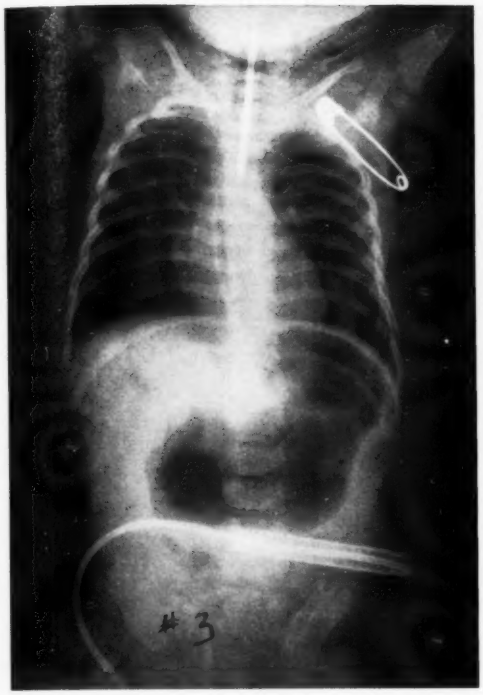

FIGURE 4. Upper intestinal obstruction. Scout film of abdomen showing absence of air in most of the small and large intestines.

FIGURE 5. Film taken with the child held in the inverted position and with a thermometer held against the anal dimple, indicating the distance between this area and the end of the imperforate rectum.

the central nervous system. However, it is of some interest to note that spina bifida occulta may be indicated by the presence of an overlying abnormal growth of hair, cutaneous angioma, subcutaneous masses of fatty tissue, or dimpling of the skin over the lower spine. When any of these signs are noted, an x-ray of the spine should be made to check the integrity of the spinal column (figure 3).

Alimentary tract—Branchial cysts and fistulas usually are readily detected, but occasionally a small dimple from which a drop or two of secretion can be expressed is the only presenting sign of such malformations.

Tracheoesophageal fistula usually can be detected or ruled out readily by passing a soft rubber catheter down the esophagus to the stomach, making certain that the catheter does not turn on itself when it encounters a blind pouch, to give a false result. An infant who has a tracheoesophageal fistula will, of course, vomit immediately after feeding and usually will present evidence of excessive secretion from the upper respiratory tract, but it is to be hoped that the defect would be detected before this happens. The obvious importance of early recognition of these abnormalities of the gastrointestinal tract is that they are particularly amenable to corrective surgical procedures during the first 48 hours of life, and the success of such procedures is almost inversely proportional to the delay before they are carried out.

Congenital bands, atresia and malrotation of the intestines usually can be suspected, not only because of the frequent association of polyhydramnios in the mother and upper intestinal obstruction in the infant but also because of the unusual distention of the infant's abdomen. Scout films show the absence of air in the nonpatent parts of the intestinal tract

FIGURE 6. Large diaphragmatic hernia. Left side of chest filled with intestinal loops.

(figure 4). The so-called Farber test (examination of the meconium for the presence of epithelial structures) does not definitely rule out obstruction, for a positive result may be obtained despite an obstruction higher up in the intestinal tract.

In the terminal gastrointestinal tract, imperforate anus is a relatively frequent finding. The recent tendency to take temperature readings in the groin rather than in the rectum will, I am afraid, result in failure to detect many such cases. The physician should routinely examine the anus and carry out a digital examination of the rectum (figure 5).

Respiratory tract—Most abnormalities involving the respiratory tract are evidenced by marked difficulty in breathing. A properly made chest x-ray may solve the problem of dyspnea or cyanosis or both. One of the most confusing physical signs is the dyspnea which results when intestinal contents intrude into the thoracic cavity through a diaphragmatic hernia (figure 6). Here, again, prompt diagnosis and immediate surgical treatment usually are lifesaving. Other congenital abnormalities such as cystic disease of the lungs, congenital pneumothorax and congenital atelectasis usually require both a careful physical examination and accurate x-ray studies for their detection.

Circulatory system—Cyanosis does not always mean congenital heart disease, nor is congenital heart disease always attended by cyanosis, particularly at birth. Here our most helpful sign, the presence or absence of a murmur, may be equally deceptive. The murmurs created by the temporarily patent ductus arteriosus may disappear in a few hours or days, and fatal congenital lesions may produce no murmurs whatever. Moreover, congenital heart diseases which generally are associated with cyanosis, such as tetralogy of Fallot, may not present cyanosis while the ductus is still open. Coarctation of the aorta may be extremely difficult to detect because of the difficulty in palpating the femoral pulsations in the newborn infant. Once again, roentgenographic study of the chest, preferably both an anteroposterior and a lateral view, may be of real value in indicating the presence of such gross anomalies as a trilocular heart and fibroelastosis fetalis (endocardial fibrosis) (figure 7). Double aortic arch and other anomalies of the arch also must be considered (figure 8).

Bones and joints—Malformation of the bones and joints usually is apparent clinically, but occasionally congenital absence of the fibula may be detected only roentgenographically. The accompanying defect of the foot

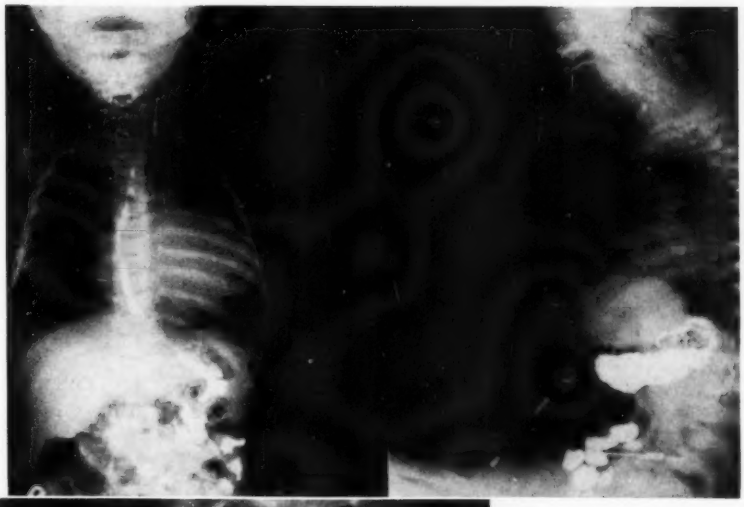

FIGURE 7. Fibroelastosis fetalis. Greatly enlarged heart.

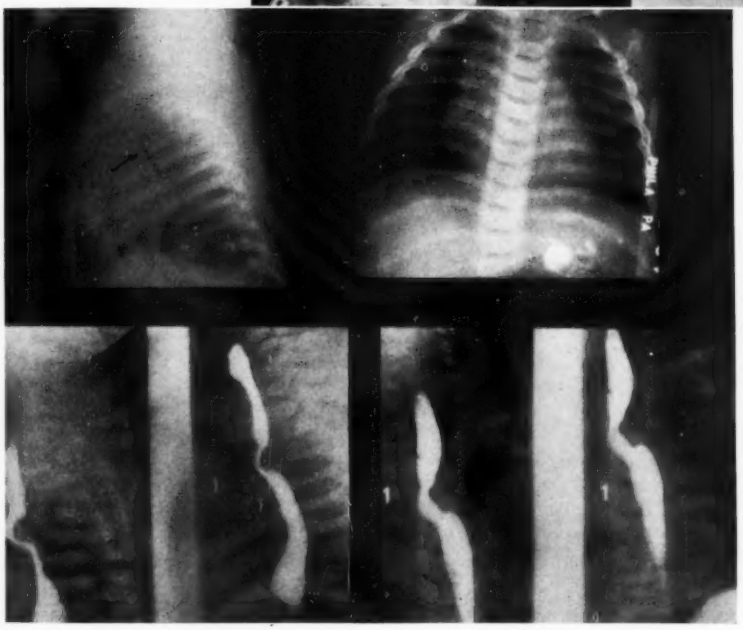

FIGURE 8. Double aortic arch. Notching of esophagus due to pressure.

usually is sufficiently marked to indicate a need for x-ray studies.

Urinary tract—Malformations of the urinary tract are of particular importance because of the impossibility of visualizing them. Recently it was demonstrated that congenital abnormalities of the external ear not uncommonly are associated with such urologic anomalies. When malformation of the ear is observed, one should not only examine the abdomen carefully by palpation and percussion but also obtain an intravenous urogram. As already suggested, the presence of oligohydramnios in the mother is a strong indicator of the possibility of such abnormalities, and when this condition has been detected one

FIGURE 9. Hypospadias (penile type).

FIGURE 10. Hurler's disease (lipochondrodystrophy).

should perform routine analyses promptly, estimate the urea nitrogen level, and obtain intravenous urograms. Horseshoe kidney, hydronephrosis and other gross anomalies of the urinary tract may be detected by palpation, but in most cases urinary anomalies can be recognized only by a more complete study.

Genitalia—We must not forget to look for anomalies of the genitalia. Epispadias, hypospadias (figure 9), cryptorchism and hermaphroditism can be detected only by careful examination. A markedly enlarged clitoris should always arouse suspicion of the adrenogenital syndrome.

Endocrine defects—Of even greater importance in terms of recognition of congenital abnormalities are those which do not present any cardinal symptoms on physical examination. Among these is congenital failure of development of the thyroid gland, resulting in athyrotic cretinism, which can be detected only by careful laboratory studies following a high index of suspicion. Also in the endocrine field are congenital diabetes and gonadal dysgenesis with all the complications such conditions entail.

Genetic anomalies—In the genetic group are many congenital abnormalities including mucoviscidosis or pancreatic fibrosis, which may be manifested in the newborn infant as meconium ileus and is possibly diagnosable by x-ray but again only when there is a high degree of suspicion of its probable presence.

Inborn errors of metabolism—Of even greater difficulty from a diagnostic standpoint are inborn errors of metabolism. Their importance increases when we realize that their recognition may well lead to their correction. Among these defects is so-called phenylketo-

FIGURE 11. Marfan's syndrome.

nuric oligophrenia. Here, a family history is extremely important, but this may not be available. In recent months we have noted a tendency to check the urine of infants routinely with litmus paper impregnated with ferric chloride, particularly after the sixth week (when the test is more likely to be positive). So the typical green test may suggest the presence of this condition in time to correct it by adequate diet and therapy.

Closely allied to this is the recently discovered "maple syrup" urine disease in which there is a branched-chain ketoaciduria. This also seems to be due to a block in the metabolic degradation of certain amino acids, and since at birth the central nervous system symptoms may not be too apparent we must depend primarily on the maple-sugar odor of the urine. This can be accentuated by acidification with dilute sulfuric acid. If the dinitrophenylhydrazine test is used, it may not be possible to distinguish between this condition and phenylketonuria, but the ferric chloride test does show some definite differences. Since the establishment of routine ferric chloride testing of urine, a number of unsuspected cases of phenylketonuria have been detected. Since the publication of information regarding "maple syrup" urine disease, there has been a greater degree of attention to the odor of the diaper for the detection of this disease.

In the same category one might include Wilson's disease (hepatolenticular degeneration) and possibly celiac disease. Another relatively frequent condition is defective hexose metabolism in the form of galactosemia, sometimes referred to as congenital galactosuria. Here, again, without a careful differential study of the reducing substances excreted in the urine the diagnosis may not be made until considerable damage has been done.

Among errors of protein metabolism, we must bear in mind familial idiopathic dysproteinemia, hemophilia A and hemophilia Ahg as well as hemophilia B (Christmas disease or plasma thromboplastin component deficiency), hemophilia C, and, of course, agammaglobulinemia. Abnormal hemoglobins, thalassemia major and minor, and the sickle-cell variants all enter the picture as problems of defective hemoglobin synthesis. In addition, abnormal amino acid metabolism may lead to alkaptonuria, tyrosinosis, albinism, cystinosis and a number of less common clinical entities.

Errors in carbohydrate metabolism include Hurler's disease (lipochondrodystrophy) (figure 10), Marfan's syndrome (figure 11), osteogenesis imperfecta, and collagen storage disease as well as those already mentioned. In the category of errors of lipid metabolism are idiopathic hyperlipemia, defective cholesterol metabolism, and the vast group of conditions including Niemann-Pick disease, Gaucher's disease and Tay-Sachs disease. Finally, errors in pigment metabolism include the various porphyrias, defective bilirubin excretion, and defective hemoglobin pigment as well as hemochromatosis.

Detection of Glaucoma in United States Air Force Personnel

JEROME DERSH*

Reading, Pennsylvania

Glaucoma accounts for approximately 12 per cent of the blindness in the United States. At present, nearly one million people have undiagnosed glaucoma. Early detection of glaucoma is the most important factor in preventing loss of vision.

Tonometry has proved to be the best procedure for detecting early glaucoma; it is recommended as a part of every routine physical examination.

The author reports on results of routine tonometry performed on 1000 air force personnel; previously undetected glaucoma was revealed in 10 patients; the disease was suspected in 12 other patients.

JEROME DERSH

GLAUCOMA is an insidious condition responsible for approximately 12 per cent of the blindness in this country today.[1] It has long been known that the most important factor in preventing loss of vision from glaucoma is early detection of this disease. At present in the United States, about 2 per cent of the adult population more than 40 years of age (nearly one million people) have undiagnosed glaucoma.[2,3]

Since 1951, when the first mass glaucoma survey was reported by Brav and Kirber,[4] numerous reports on mass screening for glaucoma in various parts of the United States and Canada have appeared in the literature (table 1).[1,3-14] These surveys have been confined to the civilian population. In the armed forces, officers and enlisted personnel must submit to periodic physical examinations, which provide an excellent opportunity for use of routine tonometry for the early detection of glaucoma. It is the purpose of this paper to report the results of the use of routine tonometry performed as part of the annual physical examination of 1000 United States Air Force officers and enlisted men between 35 and 64 years old stationed at Westover Air Force Base, Massachusetts. Approximately

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TABLE 1

GLAUCOMA SURVEYS REPORTED IN THE UNITED STATES AND CANADA

DATE	PATIENTS		RESULTS OF ROUTINE TONOMETRY (PER CENT OF CASES)
	Age (Years)	*Number surveyed*	
1949[2]	More than 45	720	Definite glaucoma, 2.6
1950[3]	More than 40	10,500	Intraocular hypertension, 2.7
1951[4, 6]	More than 40	10,000	Definite glaucoma, 1.53 Borderline glaucoma, 0.7
1952[7]	More than 40	238	Intraocular hypertension, 2.9 (referred for investigation)
1953[1]	More than 40	12,803	Definite glaucoma, 2.0
1954[8]	More than 40	1000	Intraocular hypertension, 1.7
1955[9]	More than 40	1000	Definite glaucoma, 1.9
1956[10]	8 per cent less than 40; 92 per cent more than 40	13,155	Definite glaucoma, 2.1
1957[11]	More than 40	1,220	Intraocular hypertension, 1.7 (referred for investigation)
1957[12]	More than 40	2000	Definite glaucoma, 2.0 Borderline glaucoma, 0.4
1957[13]	30 per cent less than 40; 70 per cent more than 40	964	Definite glaucoma, 3.1
1958[14]	More than 40	2000	Definite glaucoma, 1.5 Borderline glaucoma, 0.4

one-half of the men tested were 40 years old or younger (figure 1).

Incidence

The incidence of undetected glaucoma in all the series indicated in table 1 ranges between 1.7 and 3.1 per cent, with an average slightly greater than 2.2 per cent. In almost every survey, however, only patients more than 40 years of age were examined. Since the incidence of glaucoma increases with age, an even higher percentage would be expected in a series consisting chiefly of persons in the sixth or seventh decade of life. It is interesting to note that Phelps[5] believed that "some of the variation in statistics recorded is due to variations in the effort made to diagnose the condition. Those making more serious attempts to find glaucoma find a higher incidence, with the age of onset lower and the proportion of cases of simple glaucoma higher."

It should be emphasized here that in all the published surveys thus far, no untoward reactions from sensitivity to the anesthetic or complications from corneal injury with the use of the tonometer have been reported.

Method of Detection and Results

The United States Air Force requires annual physical examinations of all personnel on flight status, regardless of age, and of all nonflying personnel more than 40 years old. It was decided to perform tonometry on all individuals more than 35 years of age as part of the routine physical examination and ophthalmologic workup, which consists of testing visual acuity, evaluating muscle balance, determining fusion, and funduscopy. For the purpose of accumulating these statistics, I used a standardized Schiötz tonometer for all tonometry readings. Those individuals with an intraocular tension greater than 25 mm. mercury (readings below 4.0 on the Schiötz scale with the 5.5 gm. weight or below 6.0 with the 7.5 gm. weight) were recalled for

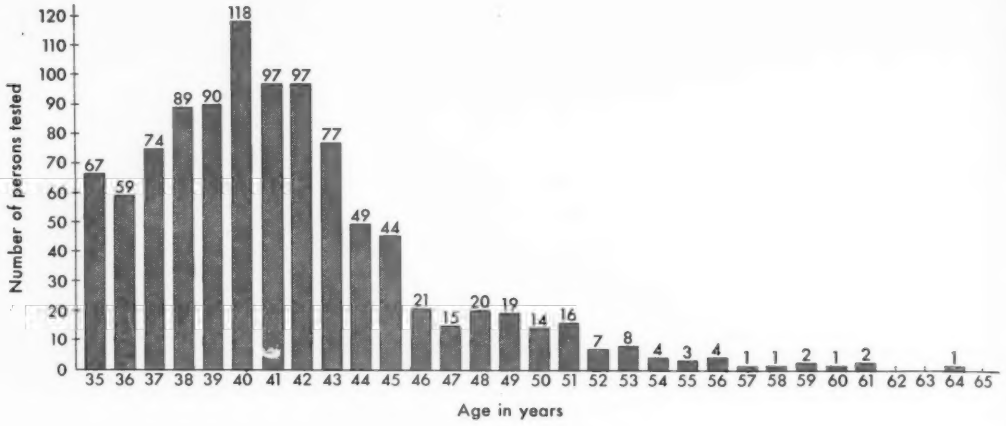

FIGURE 1.

further tonometric studies. When intraocular pressure exceeded 25 mm. of mercury on three or more occasions, examination of the visual fields and gonioscopy were performed. If the angle of the anterior chamber was found to be open, a water-provocative test was done.

The following criteria were employed in making a positive diagnosis of glaucoma: (1) an intraocular pressure consistently greater than 25 mm. of mercury on three or more examinations, and (2) a rise of 6 mm. of mercury or more within one hour in the water-provocative test, if the angle of the anterior chamber was open on gonioscopy. Visual acuity, results of funduscopy, and visual fields were essentially within normal limits and were, therefore, of no diagnostic value in this series.

Those individuals whose only ocular abnormality was an occasional elevation of intraocular tension to 28 mm. of mercury or less in one or both eyes or who exhibited a difference of 5 mm. or more between the two eyes were classified as "glaucoma suspects." Patients having a family history of glaucoma also were placed in the latter category. These patients are to be checked with tonometry every six months.

Ten of the 1000 individuals tested (1.0 per cent) were found to have early or borderline glaucoma; 12 persons (1.2 per cent) were classified as glaucoma suspects. Seven of the 10 patients in whom early glaucoma was diagnosed were between the ages of 35 and 44 years (table 2).

Discussion

The results of this study support the contention of numerous authors that the practice of routine tonometry presents the best method today for the early detection of unrecognized glaucoma.[15] The incidence of glaucoma as reported in this series, although lower than the 2 per cent average reported by others, remains significant, since 86 per cent of the persons subjected to tonometry were 45 years of age or less. It is to be noted, therefore, that even

TABLE 2

AGE DISTRIBUTION OF PATIENTS WITH DETECTED GLAUCOMA

AGE (YEARS)	PATIENTS	
	Number examined	*Number with glaucoma*
35-39	379	3
40-44	438	4
45-49	119	1
50-54	49	1
55-59	11	0
60-64	4	1
TOTAL	1000	10

in the relatively young age group seen in the military service, borderline and early cases of glaucoma can be detected if searched for systematically. For this reason, Gundersen,[2] Vaughan and associates,[9] and Zeller and Christensen[8] have advocated the introduction of routine tonometry as a standard part of the physical examination in all branches of the military service.

Tonometry is a simple test which causes the patient little or no inconvenience and takes but a few minutes to perform. It is hoped that general physicians in both civilian and military life will employ tonometry as a routine part of physical examinations, so that unnecessary blindness due to undetected glaucoma may be prevented. To aid in this objective, Berens and Tolman[3] have created a new, simplified intraocular hypertension indicator which is relatively inexpensive and gives direct readings of the intraocular tension in terms of low, normal or high. Ojers[16] has explained how to use the tonometer and has conveyed the importance of routine tonometry to the general practitioner in his practice.

A most practical and effective approach to this problem is presently being carried out by 35 medical schools[14] in which the undergraduates are being taught to perform tonometry routinely on all patients more than 40 years old. Zeller and Christensen[8] attempted to do this with the interns at their hospital; however, after leaving the eye service, not a single intern made a tension test during the remainder of his internship. It would seem, therefore, that the successful teaching of the value of routine tonometry rests with the medical school and its faculty.

Summary and Conclusions

1. The most important factor in preventing loss of vision from glaucoma is early detection.

2. The results of surveys conducted to detect glaucoma in the past decade are reviewed.

3. The results of routine tonometry performed as part of the annual physical examination of 1000 United States Air Force officers and enlisted personnel are reported.

4. Previously unrecognized early or borderline glaucoma was detected in 10 patients (1.0 per cent); the ages of seven of these patients ranged from 35 to 44 years.

5. Twelve patients (1.2 per cent) were classified as "glaucoma suspects," and were to be re-evaluated every six months.

6. General practitioners, internists and industrial physicians are urged to do tonometry measurements on all persons more than 35 years old as part of routine examinations.

7. A critical need exists for the adoption of tonometry as a standard part of the annual physical examination of all personnel more than 35 years old in the United States Air Force as well as in the other branches of the armed forces.

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First-Aid Treatment of Scalds and Burns by Water Cooling

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Experimental and clinical evidence has demonstrated that water cooling is an effective first-aid treatment for scalds and burns. Experimental studies are described which indicated that it reduces the mortality rate and the severity of local pathologic changes, improves tissue regeneration and arrests degeneration of underlying tissues; the experiments, using rats as the test animals, showed further that clothing enhances the ill effects of scalding. A provisional outline of treatment for minor burns and scalds, chemical burns, and major burns and scalds in man is presented.

ICELANDERS have used cold water in first-aid treatment of burns, scalds and sprains for a very long time. In the United States[1] and in Germany this modality was used to some extent during the nineteenth century.

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As a boy, some 45 years ago, I was taught by my mother to immerse burns and sprains immediately in cold water, milk, whey, snow or sea water (whichever was closest at hand) and to keep the burned or sprained area in the cooling medium until smarting and pain were gone. My mother said this method had been used widely when she was young and that a doctor was not called unless a burn was severe or major complications arose. If, after cooling, some redness of the skin remained, a fatty ointment, often made mainly from local herbs, usually was applied. If ulcers formed, they often were covered with a heavy layer of granulated sugar (osmosis?) or fresh leaves of herbs.

I have often seen cases of burns and scalds that have seemed to benefit from cold-water treatment. For example, in 1948 I examined a 40 year old woman whose right hand and arm had been burned when she fell into a pot of boiling milk at the age of two years. The burned area extended to the axilla. A woman who was present put the injured extremity into a bucket of cold water immediately. The cold water reached only to the elbow. Thirty-eight years later, the back of the hand had a smooth

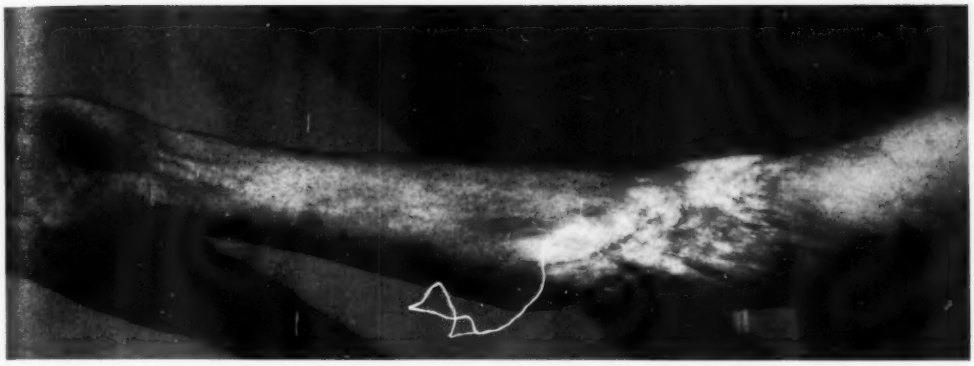

FIGURE 1. Photograph of right arm of 40 year old woman described in text. Note healthy appearance of forearm, which was immersed in cold water after being burned, in contrast to the upper arm, which was not so treated.

superficial scar and the rest of the hand and the forearm seemed quite normal, but the arm from elbow to shoulder was disfigured by deep scars (figure 1). The greatest circumference of the injured upper arm was only 23 cm. compared with a circumference of 24.5 cm. of the left arm, in spite of the fact that the woman is right-handed.

In 1928, when I was a medical student, I tried to investigate the effect of cold water on coagulation of egg albumen by boiling hen's eggs and immersing half of them immediately in tap water until they became cold and allowing the other half to cool on a wooden table at room temperature. The water-cooled eggs were always less coagulated. I repeated the procedure using eggs covered with pieces of cloth to simulate human clothing, keeping the cloth on the eggs until they were cold, and the difference in coagulation was even more pronounced. These observations indicated that clothing soaked in hot water increases and prolongs the ill effect (coagulation) of scalds on living matter (protein).

Experimental Observations in Rats

In 1954 I had an opportunity to conduct animal experiments on the effect of immediate cold-water treatment of scalds at the University of Glasgow, with the aid of a grant from the British Council. Readers who are interested in a more detailed account of these experiments will find it in the article, "Observations and experiments on the immediate cold-water treatment of burns and scalds," in the July 1959 issue of the *British Journal of Plastic Surgery*. At first I tried to follow the procedures used by other investigators in experiments with hypothermia in burns and scalds, but I soon felt that I had to go my own way. By trial and error, suitable procedures were developed for later experiments, on which the ensuing discussion is based.

The animals used were 186 young albino rats. General anesthesia was induced, and the hair on the back and flanks was clipped. Then this area was either covered with one layer of surgical lint and two layers of bath towel (a "triple clothing" designed to simulate human clothing) or left bare. The superficial skin temperature of the area to be scalded was measured just before the experiments and found to average 33.6° C. Twenty per cent of the body surface area was immersed in water at 83° C. for 30 seconds. The control animals were then placed in their cages, the "clothing" of those which were "clothed" being removed at varying intervals. The scalded area of the "treated" rats was immersed in cold water immediately, and the "clothing" likewise was removed at varying intervals. Superficial temperatures of the scalded area were determined for both groups immediately after withdrawal from the hot water and periodically thereafter (table 1).

TABLE 1

AVERAGE SUPERFICIAL SKIN TEMPERATURE (CENTIGRADE) OF RATS BEFORE AND AFTER SCALDING OF 20 PER CENT OF BODY SURFACE AREA FOR 30 SECONDS (83° C.)

AVERAGE WEIGHT (GRAMS)	AVERAGE SUPERFICIAL SKIN TEMPERATURE (CENTIGRADE)																			MORTALITY RATE
	Before	*0 sec.*	*20 sec.*	*30 sec.*	*40 sec.*	*50 sec.*	*60 sec.*	*70 sec.*	*80 sec.*	*90 sec.*	*100 sec.*	*110 sec.*	*120 sec.*	*2.5 min.*	*3 min.*	*3.5 min.*	*4 min.*	*4.5 min.*	*5 min.*	*10 min.*	
Experiment X. C.* "Triple clothing" (two layers bath towel, one layer surgical lint) retained for five minutes after scalding																				
189	33.8	59.5	58.5	57.8	57.0	56.0	55.0	54.1	53.2	52.5	51.7	51.0	50.3	48.3	46.3	44.9	43.6	42.4	41.2	. . .	100 per cent
Experiment XI. T.* "Triple clothing" removed immediately in water at 15° C., taking 15 to 20 seconds. Animal then removed from water																				
172	33.7	58.5	36.9	36.9	36.7	36.3	36.1	35.8	35.5	35.2	34.8	34.6	34.4	33.8	33.3	33.0	32.7	32.5	32.1	. . .	70 per cent
Experiment XII. T. "Triple clothing" removed immediately in water at 18° C., taking 10 to 20 seconds. Animal kept in water for total of 25 seconds																				
165	33.3	59.0	30.2	31.0	31.9	32.3	32.4	32.5	32.4	32.5	32.5	32.6	32.6	32.3	31.9	31.8	31.5	31.3	31.3	. . .	30 per cent
Experiment XIII. T. Immediate removal of "triple clothing" during total immersion of 25 seconds in water at 22° C.																				
220	33.6	59.7	32.5	28.7	30.5	31.6	31.9	32.0	32.1	32.2	32.3	32.3	32.4	32.3	32.2	32.2	32.0	31.9	31.8	. . .	0 per cent
Experiment XIV. T. Immediate removal of "triple clothing" during total immersion time of 25 seconds in water at 25° C.																				
179	33.7	59.9	31.1	30.0	31.8	32.6	32.9	32.8	32.7	32.6	32.5	32.4	32.3	31.9	31.5	31.1	30.8	30.6	30.3	. . .	10 per cent
Experiment XV. T. Immediate removal of "triple clothing" during total immersion time of three minutes in water at 25° C.																				
193	33.7	58.2	28.6	29.3	29.6	30.0	30.2	30.2	30.2	30.2	30.1	30.0	30.1	29.6	29.5	28.6	28.6	28.6	28.4	. . .	0 per cent
Experiment XVI. T. Immediate removal of "triple clothing" during total immersion time of five minutes in water at 25° C.																				
240	33.6	62.8	29.3	30.6	31.3	30.6	30.8	30.9	31.0	31.0	31.1	31.1	31.1	31.2	31.1	31.3	31.1	30.7	30.6	. . .	20 per cent
Experiment XVII. T. Immediate removal of "triple clothing" during total immersion time of five minutes in water at 30° C.																				
161	33.6	63.9	33.0	33.1	33.1	32.9	32.9	32.9	33.0	32.8	32.6	32.7	32.5	32.9	32.9	32.8	32.8	33.0	33.0	. . .	20 per cent
Experiment XVIII. T. Immediate removal of "triple clothing" during total immersion time of 10 minutes in water at 30° C.																				
175	33.6	62.8	32.7	32.6	32.5	32.5	32.4	32.2	32.1	32.1	32.1	32.1	32.1	32.1	32.1	32.1	32.0	32.0	32.0	31.0	10 per cent

*C, control animals; T, "treated" animals.

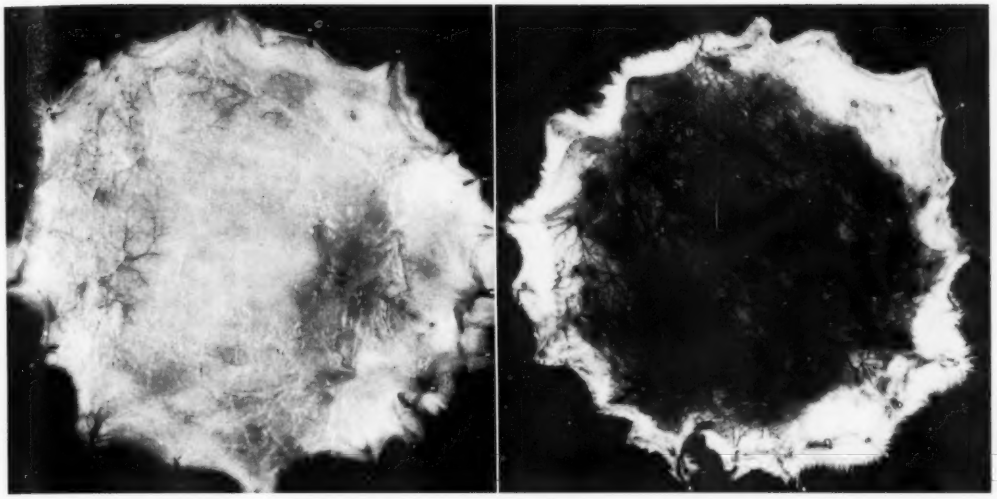

FIGURE 2. Inner surface of skin of rats 15 hours after scalding of 20 per cent of the body surface area for 30 seconds at 83° C. "Triple clothing" retained for one and a half minutes.

Left. Skin of rat treated with cold water immediately after scalding.

Right. Skin of control animal.

In the first experiments ice water (0° C.) was used. The mortality rate was higher among the "treated" rats and death came sooner, but the pathologic changes in the scalded areas were much less pronounced than in the control animals. This observation led to the conjecture that the cause of the higher mortality rate was a cold shock in addition to the heat shock. In the hope that the beneficial effects of the local water cooling could be achieved without jeopardizing the animals by cold shock, the temperature of the cooling water was raised gradually. As the temperature was raised, the mortality rate decreased steadily, and when a water temperature of 22 to 25° C. was reached the mortality rate for the "treated" rats had declined to 10 to 0 per cent in contrast to the 100 per cent mortality of the control animals with "clothing" (table 1). In later experiments in which the cooling water was almost warm (22 to 25° C.) the local changes continued to be much less pronounced in the "treated" rats than they were in the control animals.

Almost 200 preparations were taken from scalded areas for microscopic examination. The microscopic findings seemed to correlate closely with the macroscopic observations. The scalded area in the control animals showed severe edema, hyperemia and dilatation of blood vessels shortly after the scalding, whereas there were only a few slightly hyperemic spots in the cutis of the scalded area in the "treated" rats (figure 2). The "clothing" definitely increased the pathologic changes, in direct proportion to the length of time it was kept on the body. Seldom did the macroscopic changes extend deeper than the subcutis of the "treated" rats, whereas in the control animals the pathologic process seemed only superficial initially but gradually extended deeper into the tissues so that after 16 to 21 days it reached into the muscles and sometimes through the peritoneum, forming adhesions with adjacent intestine. The process always was most pronounced at the center of the burn, forming a funnel-shaped necrosis or gangrene (figure 3).

On the twenty-first day of each experiment, when the surviving animals had to be killed (animal license regulations), almost all the controls had died or had such far-advanced

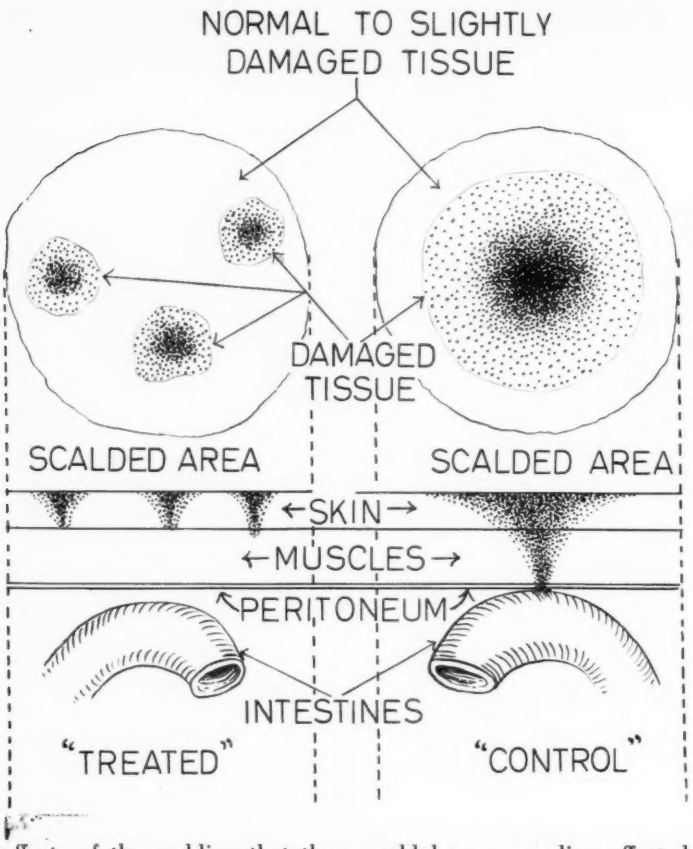

FIGURE 3. Diagram showing patchy appearance of scalded skin and underlying tissues with (*left*) and without (*right*) cold-water treatment. Upper portion of diagram illustrates the inner surface of scalded skin, the lower portion a section through the peritoneal cavity.

effects of the scalding that they would have died in a short time. In contrast, many of the "treated" rats were alive and well. The scalded area had healed or was covered with healthy granulations. The newly formed skin appeared normal except that it was partially denuded of hair (in places it was covered with thick short hair). In other words, the prognosis seemed to be healing per primam in almost all cases. In the controls the entire scalded area was always universally affected, predominantly so near the center of the burn, but in the "treated" rats there were only patches of pathologic involvement with healthy-looking interspaces (figures 2 and 3).

Although these experiments have been done with only a relatively small number of animals and in many ways fall short of their intended scope, I shall take the liberty of enumerating the benefits I think the use of water cooling effected and the observations I consider significant.

1. Lower mortality rate among "treated" animals.

2. Less severe local pathologic changes.

3. Better, more rapid and more complete regeneration, which seemed to occur not only from the periphery of the scalded area, as in other types of burn, but also from the healthy spaces that were present within the scalded area (figures 2 and 3).

4. Continued burning, sometimes for a long time, of underlying tissues by clothing initially soaked in scalding fluid (water), so long as the clothing was hot enough.

5. Great danger in using a very cold medium, e.g., ice water at 0° C., to cool scalded areas, except in minor burns.

6. Surprising effectiveness of lukewarm cooling water (22 to 25° C.) in reducing

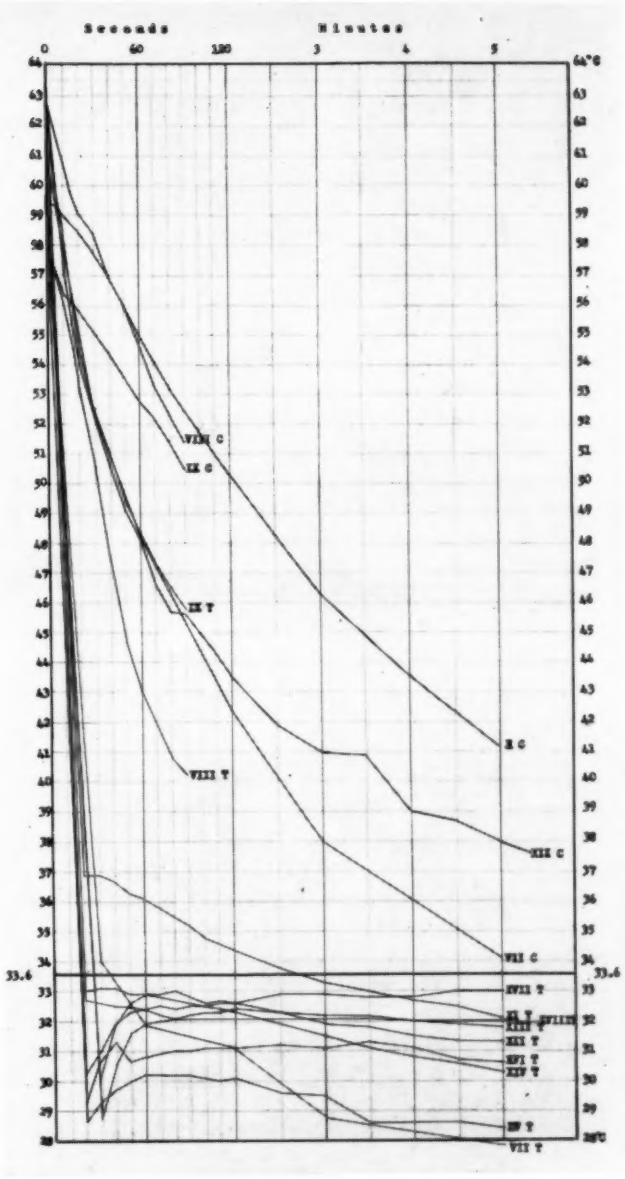

FIGURE 4. Drop of average superficial skin temperature after scalding of 20 per cent of body surface area of rats at 83° C. for 30 seconds (C, controls; T, "treated" animals).

Experiment VII: "Single clothing" retained for five minutes after scalding. C. Early mortality 20 per cent. T. Immediate ice water for one minute. Early mortality 50 per cent.

Experiment VIII: "Double clothing" retained for 1.5 minutes after scalding. C. Early mortality 33.3 per cent. T. Immediate ice water for 40 to 80 seconds. Early mortality 66.6 per cent.

Experiment IX: "Triple clothing" retained for 1.5 minutes after scalding. C. Early mortality 100 per cent. T. Immediate ice water for 10 to 20 seconds. Early mortality 50 per cent.

Experiment X: C. "Triple clothing" retained for five minutes after scalding. Early mortality 100 per cent.

Experiment XI: T. "Triple clothing" removed immediately in water at 15° C. (taking 15 to 20 seconds). Animal then removed from water. Early mortality 70 per cent.

Experiment XII: T. "Triple clothing" removed immediately in water at 18° C. (taking 10 to 20 seconds). Animal retained in water for 25 seconds. Early mortality 30 per cent.

Experiment XIII: T. Immediate removal of "triple clothing" during immersion for 25 seconds in water at 22° C. No early mortality.

Experiment XIV: T. Immediate removal of "triple clothing" during immersion for 25 seconds in water at 25° C. Early mortality 10 per cent.

Experiment XV: T. Immediate removal of "triple clothing" during immersion for three minutes in water at 25° C. No early mortality.

Experiment XVI: T. Immediate removal of "triple clothing" during immersion for five minutes in water at 25° C. Early mortality 10 per cent, late mortality (13 days) 10 per cent.

Experiment XVII: T. Immediate removal of "triple clothing" during immersion for five minutes in water at 30° C. Early mortality 20 per cent.

Experiment XVIII: T. Immediate removal of "triple clothing" during immersion for 10 minutes in water at 30° C. Early mortality 10 per cent.

Experiment XIX: C. No "clothing." Scalded area wiped gently with soft bath towel and allowed to dry in air. No early mortality.

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superficial skin temperature (about equal to ice water at 0° C.) (figure 4).

7. Close correlation between microscopic and macroscopic pathologic changes in scalded tissues.

8. Much less secondary infection.

9. Arrest by water cooling (as yet unexplained) of pathologic degeneration of underlying tissues, which was so apparent in the control animals and lasted for weeks.

10. Continuing degeneration of underlying tissues in control animals for at least 21 days after scalding.

Water Cooling as First-Aid Treatment of Burns and Scalds in Man

The question arises whether water cooling should be used as first-aid treatment of burns and scalds in human beings. The cooling of overheated tissues, like the cooling of all other things, occurs by radiation of heat to the surroundings: (1) outside the body to clothing, air, fluid (e.g., water), ointments, etc. and (2) within the body to surrounding tissues, lymph and blood. Very hot clothing must therefore prolong and increase the burning or scalding of tissues. Bandages and ointments applied immediately to a burn or scald probably inhibit the cooling of the tissues and are therefore undesirable. Cooling by water is much faster than cooling by equally cool air.

Doctors agree that treatment of extensive burns and scalds should begin as soon as possible in order to combat shock, but many of them advise against any treatment until the patient is in the hospital. This may mean a delay of many hours or even days, and by that time the patient may have died from shock.

The chief objection to any first-aid treatment is that the danger of secondary infection is increased. Whether this is a more serious hazard than the danger of similar infection in a hospital is open to question, in view of the conclusions of Colebrook and associates.[2] In any event, the experiments I have described showed clearly the greatly reduced incidence of infection in the "treated" rats.

Some writers recommend administration of morphine or a sedative immediately after burns and dressing of the burned areas with sterile dressings or clean linen. If the burn (scald) is cooled immediately with water, it will be unnecessary in most cases to use any sedation because water cooling has pronounced anodyne effects. In extensive burns or scalds, however, where the cooling water should not be colder than 22 to 25° C., sedation may be necessary, possibly in the form of phenobarbital plus some analgesic agent such as aspirin, codeine, pethidine (meperidine) or morphine, according to the intensity of the pain. If the water is cold enough it completely inhibits the urge to scratch the burned or scalded skin and thereby reduces the hazard of secondary infection.

Another objection by doctors to first-aid treatment is the use of different ointments and lotions which many people apply in order to "do something." They are difficult to clean away. This objection does not apply to water.

In 1936 Rose[3] reported good results with initial cold-water treatment of burns. In 1960 Shulman[4] also described good results with this method. He used water at 5 to 13° C. in 150 cases of burns (of first, second and even third degree) involving less than 20 per cent of body surface. Shulman's series included not only thermal burns but also chemical and electric burns, and in all these kinds of burns there was almost complete abolition of pain as well as a reduction in the duration of treatment and the number of office visits "to about one-third of that of patients treated otherwise."

Suggested Outline of First-Aid Treatment of Burns and Scalds

While I realize that further investigation is required to determine the optimal temperature and duration of water cooling in both animals and man, I shall take the liberty of outlining a provisional first-aid treatment for burns and scalds.

If hair or clothing is on fire, smother the fire immediately with anything available—coats, blankets, water or any harmless, nonflammable fluid, or snow.

Minor burns and scalds—1. Run cold tap water over the burn or immerse it in cold water, milk, sea water, soft drinks or any other clean, harmless fluid close at hand or in

snow or ice (the latter possibly from the refrigerator). *Note:* Although cooling of the burned or scalded area may be started with any one of the cooling media listed, one should change to cool, clean water as soon as possible. If running water (showers, hoses, taps) is used, care must be taken not to use too much pressure to spray the injured tissues and further damage the already damaged skin. Keep the cooling fluid cold enough to provide the greatest relief from pain, and do not withdraw the burned area from the cooling medium until pain and smarting have completely disappeared.

2. If blisters have formed, avoid breaking them as long as possible.

3. Do not apply bandages or dressings except when necessary. They inhibit radiation of heat from the injured area and make the patient more uncomfortable.

Chemical burns—1. Flush the burned area thoroughly with cool water to dilute and remove the chemical and reduce pain. If the eyes are burned, flush them gently and thoroughly with cool water.

2. Call the doctor or send the patient to the hospital, informing the hospital at the same time what has happened and what has been done for the patient.

Major burns and scalds—1. If the hair or clothing is afire, smother the fire at once.

2. Let the patient lie down, preferably in a warm place to lessen exposure to cold and the possibility of shock.

3. Apply cool water immediately to the burned area, soaking any hot clothing covering it. The water may be applied by immersion in a large basin or bathtub, by pouring from a jug or bucket, by shower, tap or hose, or by repeated dipping or wet, cold compresses for face, neck and trunk.

4. When garments have been cooled enough to permit easy handling, cut away the clothing very gently and lift it from the body. Do not pull off any clothing (stockings, gloves, pants, etc.). Never spare the garment; spare the skin. Do not break or cut blisters. If clothing adheres to injured skin, do not remove that part of it; cut around it and leave it alone.

5. When the initial cooling and removal of burning or scalding clothes have been completed, some time should be taken to *think* about further treatment.

a. The burned or scalded areas must be constantly cooled.

b. The victim must be as warm and comfortable as possible. Cold, wet compresses should be constantly applied to burned areas on the head, neck or trunk. Clean, dry clothing should cover the rest of the patient to keep him comfortably warm, but not so warm as to cause perspiration.

If the patient is conscious and asks for something to drink, preferably warm, give it to him, but do not give him alcohol or stimulants. Let the patient decide how cold the cooling water should be, except when he feels chilly. If he does feel chilly, give him some hot drink or thin soup, add clothing to the unburned areas of the body (no hot water bottles) and rub them (e.g., soles of feet if cold), and raise the temperature of the cooling water to 30° C. If the burn is very extensive, even if it is superficial, the cooling water should be lukewarm (22 to 25° C.). The warmer the cooling water, the less is its anodyne effect: "It has been learned that the cold treatment must be continued until it is possible to discontinue treatment without return of pain. . . . The time required may be from 30 minutes to as long as five hours."[4]

6. Do not touch the burn with your hands.

7. If the burn requires a dressing, wash your hands carefully with soap and water before applying it.

8. Call the doctor and ask him to come. This is preferable to taking the patient to the doctor, which would force discontinuance of the cooling treatment. *Note:* The initial cooling and removal of overheated clothing must be accomplished before time is taken to call the doctor, hospital, telephone operator, ambulance or fire department.

9. Do not use any ointments.

10. If it is impossible to obtain skilled help (doctor, nurse, hospital), keep the patient as comfortable as possible, encourage him, and watch him closely.

11. When the cooling is over and the patient is relatively free of pain, it is best not to

apply dressings to the burned areas. If they are necessary, use sterile dressings or clean, soft, freshly laundered linen.

12. All major and extensive burns, even if they seem superficial, may produce the dangerous burn shock. If the victim is frightened, apprehensive, restless and pale, if the skin is cold and clammy, and breathing is rapid, shallow or irregular, the following measures should be instituted.

Keep the patient lying down with his head lower than his feet. Loosen his clothing. Keep him lightly covered and comfortably warm but not so warm that he perspires. Dissolve 1 tsp. of table salt and ½ tsp. of baking soda in a quart of water and give him a sip at a time as frequently as possible without producing nausea. Discontinue giving the solution if the patient vomits. Try by all means to keep the patient comfortable and quiet and to reduce his anxiety. Give him sedatives as required.

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Books Received

Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Reviews in this issue start on page A-161; additional listings appear on page 310.

The Premature Baby. By V. Mary Crosse, O.B.E., Consultant Paediatrician, Sorrento Maternity Hospital, Birmingham, England. Ed. 5. 266 pages with 42 illustrations. 1961, Little, Brown & Company, Boston. $7.00.

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Migraine Equivalents

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There is ample evidence that vasodilatation of blood vessels with an altered contractile state, probably following a vasoconstrictive phase, is associated with migraine.

The author discusses conditions known as migraine equivalents in which this vascular dysfunction apparently produces clinical manifestations that do not conform to the classic migraine syndrome.

In diagnosing migraine equivalents, it is most important to remember that they may be symptomatic of organic disease of the central nervous system.

LORNE D. PROCTOR

MIGRAINE was probably known to the Egyptians as early as 12 B.C., but the condition was first described adequately by the Greeks (Arateaus of Cappadocia)[1] in the first century A.D. Classically, the term migraine applies to a vascular type of headache involving only one half of the cranium, preceded by a visual aura, and accompanied by nausea and vomiting. The illness is recurrent and has a familial diathesis.

Wolff, Tunis and Goodell[2] have discussed vascular headaches extensively and have ample evidence that vasodilatation of blood vessels with an altered contractile state, probably following a phase of vasoconstriction, is the vascular dysfunction associated with migraine. The vessels involved are the internal and external carotid artery systems, the circle of Willis, and the basilar plexus. These phenomena may be seen at times in the conjunctival vessels or the retinal vessels or both on the affected side.

There is little need to dwell on the so-called migraine personality. May it be sufficient to note that hypertonicity and rigidity of thinking and behavior are outstanding components in this personality pattern. It may be comforting to migraine sufferers to point out that this

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illness has a predilection for the more mentally agile individual.

Migraine and its equivalents follow rather than accompany unusual stress.

In considering migraine equivalents, we will deal with those conditions in which the previously mentioned vascular dysfunctions apparently produce clinical manifestations that do not conform to the classic migraine syndrome. The equivalent may be present as a cranialgia followed by some other neurologic signs or symptoms, or it may consist of a purely transient episode of a localized neurologic dysfunction, e.g., neuralgia, palsy, etc. Migraine equivalents, in my experience, are as common as, if not more common than, the classic migraine "attack."

Areas of Involvement

In describing the various migraine equivalents, it is easier to understand the variety observed if one considers the multitude of areas of the central nervous system that may be locally involved in this vascular dysfunction. Should only the occipital cortex be involved, quadrantic or hemiopic visual defects will occur without subsequent hemicranialgia or vomiting (ophthalmic migraine). If the parietal lobe is the site of the vascular dysfunction, paresthesia, analgesia or various types of pain, usually limited to the face, neck and upper limbs on the contralateral side of the body, could be the predominant symptoms. Similarly, if only the motor cortex is involved, facial weakness, monoplegia or hemiplegia could result. The sensory or motor dysfunctions or both may last for minutes or hours, and it is sometimes difficult to differentiate between such migraine equivalents lasting 12 to 48 hours and so-called little strokes. Personally, I am not quite certain what many authors mean by this latter term. I assume they have in mind at least a permanent occlusion of one or more small vessels producing this neurologic clinical picture.

If the migraine-equivalent vascular dysfunction involves the temporal lobe on the dominant side, particularly the posterior portion, episodes of expressive or receptive aphasia may occur. Extensive involvement of the temporal lobe or lobes could produce varying degrees of impaired consciousness. In this latter manifestation, one must differentiate between a migraine equivalent and psychomotor epilepsy. I[3] have reported on a series of 130 cases having as a common denominator a psychomotor variant electroencephalographic pattern, and among these more than 30 per cent of the patients complained of episodic headache. Three of the 30 per cent with headaches had the classic migraine type. Ninety per cent of all patients with cranialgia in this series improved with administration of DILANTIN® sodium. This is further evidence of the close relationship between migraine and epilepsy as was first pointed out by Lennox.[4]

When the uncinate lobes are involved in this vascular process, gustatory or olfactory episodes or both may occur. In a patient who had had classic migraine attacks for many years, the attacks ceased when she was in her 40s and were succeeded by periods of smelling "strong gasolines." The most effective therapy for these attacks continued to be CAFERGOT®, the same medication she had used for the previous migraine attacks. The usual gustatory experience is an episode of metallic or sour taste.

One of the more rare migraine equivalents is manifested by an episode of spatial disorientation during which the patient feels suspended above the floor, not necessarily in the vertical position, and is confused as to right and left, etc. This is thought to be due to localization of the vascular dysfunction in the region of the angular gyrus.[5]

Much has been written about abdominal migraine. An "aura" headache may precede the abdominal cramps, nausea and possible vomiting, or it may be absent. The area of the insula may be involved in these cases. Some authors[5] have described episodes of thoracic, pelvic or precordial pain, the latter particularly associated with tachycardia and dyspnea (precordial migraine), which may be preceded or accompanied by nausea and vomiting. I find it difficult to suggest the probable localization of the central nervous system dysfunction in such cases.

Another rare equivalent is cerebellar ataxia,

which undoubtedly is the result of migraine vascular dysfunction involving the cerebellar arteries. Similarly, involvement of the basilar artery could produce vertigo, impairment of conjugate deviation of the eyes, ataxia, and finally even impairment of consciousness, e.g., confusion, through involvement of midbrain reticular formation.

Severe autonomic or hypothalamic migraine equivalents are also rare. More frequently seen are the milder forms, in which hypersalivation, rhinorrhea, dilation of pupils, hyperhidrosis, and flushing preceding or attendant with headache occur periodically.

I have not observed ophthalmoplegic migraine, but Friedman and Merritt[1] described patients with recurrent unilateral headache, accompanied by extraocular palsies. They suggested that pressure on the third cranial nerve, passing between edematous superior cerebellar and posterior cerebral arteries and on the sixth cranial nerve, passing between edematous auditory and inferior cerebellar arteries, is the basis for these extraocular palsies. The third cranial nerve is affected 10 times more often than is the sixth, and the pupil invariably is dilated. The palsies may be present for days or weeks after the headache.

Recurrent neuralgias, with or without headache, could be included in this ill-defined equivalent category. The most common of these involves the trigeminal area, probably through vascular embarrassment of the gasserian ganglion. The remaining facial neuralgias in this group could be attributed to a migraine dysfunction of the external carotid artery. They would include petrosal neuralgia, described by Gardner, Stowell and Dutlinger,[6] and Vidian neuralgia, and would appear to closely resemble histaminic cephalalgia and cluster headaches, described by Horton, MacLean and Craig.[7]

Finally, neuralgia over the distribution of the temporal artery is mentioned only to point out that transient changes in and about this vessel are associated with this complaint. Wolff, Tunis and Goodell[2] have used the changes in tissues surrounding the temporal artery in such a case to illustrate that edema and change in pain sensitivity do occur in persons with vascular headaches of the migraine type. Such a neuralgia should be differentiated from temporal arteritis. This latter "neuralgia" is progressively of longer duration, and the artery is hard, nodular and exquisitely tender.

Bell's palsy, which is known to accompany headache, may continue for hours or days after the headache has gone.

Although tension headache, the most common of all headaches (30 per cent), must be included in the differential diagnosis of migraine equivalents, it presents little difficulty. The occipital muscle mass is usually tense and tender to pressure, the headaches are not cyclic but continue for days or weeks, nausea or vomiting seldom occurs, and there is no aura present.

It is most important to remember that migraine equivalents may be symptomatic of organic rather than of functional disease of the central nervous system. Should there be any question about the cyclic nature of the dysfunction, or if there is a progressive increase in severity of consecutive episodes, a most thorough neurologic investigation, including angiography, pneumoencephalography and electroencephalography, is indicated. A migraine equivalent that fails to respond to early treatment with vasoconstrictor drugs should arouse a strong suspicion regarding the diagnosis.

In the case of precordial pain, the usual thorough cardiovascular investigation is indicated before making a diagnosis of migraine equivalent, as would be a thorough gastroenterologic investigation in the case of an abdominal migraine. Electroencephalography will assist in eliminating those borderline cases of so-called epileptiform syndromes in which the migraine syndrome is really an epileptic equivalent, requiring anticonvulsant medication, i.e., Dilantin sodium and phenobarbital, rather than vasoconstrictor drugs.

Treatment

The treatment of migraine equivalents is the treatment of migraine. Prophylaxis is important. We are usually dealing with hypertonic individuals who are experiencing dif-

ficulty adapting to their stress. The need for psychotherapy is obvious, and many can be adequately treated by supportive psychotherapy with adjustment of habit patterns and a mild relaxant, e.g., 1 gr. sodium AMYTAL® two or three times daily. Others may require interpretive psychotherapy or a lengthy, formalized psychiatric program. Ingestion of alcohol is one of the best ways to trigger a migraine equivalent.

During the attack, 1 mg. ergotamine tartrate with 100 mg. caffeine (Cafergot) is the most beneficial. This should be administered at the earliest possible stage of the attack, and if the patient cannot tolerate this medication orally because of vomiting, suppositories containing 2 mg. ergotamine tartrate with 100 mg. caffeine may be used. The maximal dose of ergotamine should be 6 to 8 mg. per day, and this program should not be repeated in less than 10 days. If parenteral ergotamine is necessary, dihydroergotamine methanesulfonate (DHE-45) is indicated. It is less likely to produce side effects, such as vomiting, cramps, tingling of hands, etc., but it has less vasoconstrictive action than ergotamine tartrate and a 1 mg. dose intramuscularly can be repeated in one hour. Ergotamine compounds are contraindicated in the presence of pregnancy, peripheral vascular disease, angina pectoris, impaired renal or hepatic function, etc.

Analgesics, e.g., acetylsalicylic acid and its combinations including, if necessary, a minimal dose of codeine, are the usual means of controlling a lengthy cranialgia.

There are many other pharmacologic preparations for treating migraine and the equivalents, such as WIGRAINE®, MIGRAL®, histamine diphosphate, DIAMOX®, OCTIN® hydrochloride, etc. Friedman and Merritt[1] have thoroughly discussed this subject in their recent textbook.

Comment

The medical problem of migraine equivalents lies in the confusion these syndromes create when the internist does not consider the vascular nature of their etiology. They may mimic, in part, intracranial disease of many types, e.g., neoplastic and vascular diseases, the neuritides, meningitides, Ménière's disease, arteritis, epilepsy, etc. The cyclic occurrence and usually episodic nature of this syndrome and the marked benefit from vasoconstrictor drugs will be of the greatest diagnostic assistance. If we are to diagnose migraine equivalents, we, of course, must think of them, remembering they may be symptomatic of organic disease of the central nervous system.

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Limp in Childhood

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If the gait of a child less than seven years old has a regularly repeated pattern, the child may be considered to have a limp.
In determining the cause of a limp, trauma always should be ruled out first.
Normal gait is analyzed and deviations from normal gait are discussed.
Common causes of limp and a methodical approach to their diagnosis are described and illustrated.

L. H. PARADIES

WHILE it is true that an experienced clinician can usually recognize an abnormal gait and name its cause in terms of a disease entity, it does not always follow that he can give less experienced colleagues a sequence of logical steps which led to his diagnosis.

In order to overcome this difficulty, which is essentially a lack of communication, he must adopt a systematic or a methodical approach to the problem at hand. A review of the fundamentals of normal human locomotion provides the framework for such an approach.

Normal Gait

The normal gait is divided into cycles, each consisting of the time during which a given extremity performs the function of weight bearing and swings through in preparation for subsequent weight bearing. During this cycle, the opposite extremity performs identical functions but at different times. The cycle in each extremity is divided into two phases, namely, the stance phase and the swing phase. Each of these phases is concerned with a particular function and has its own deviations from normal.

The stance phase—This phase of the cycle includes the entire time that the extremity is bearing weight. It consists of four components, namely, heel-strike, midstance, heel-off and toe-off (figures 1 and 2). A knowledge of these components not only will enable one to determine the part of the stance phase in which a limp occurs, but their absence or abnormal execution may enable one to determine the cause of a limp.

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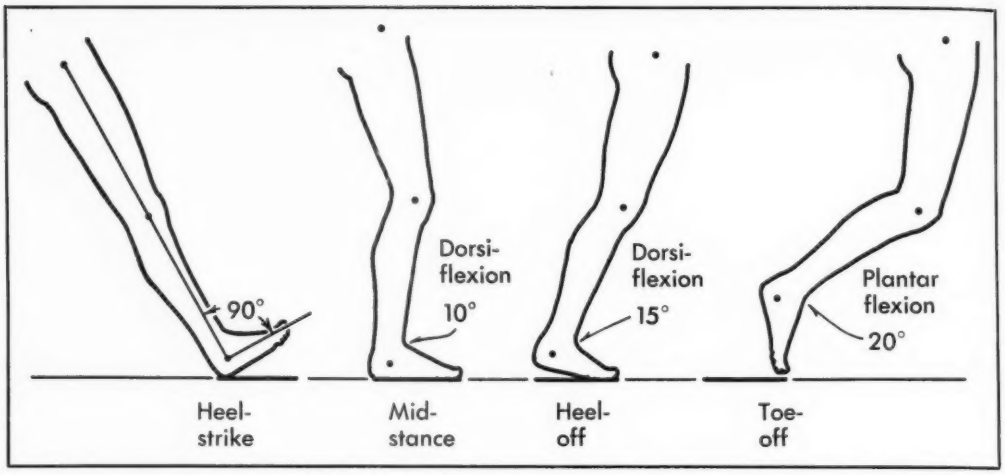

FIGURE 1. Components of the stance phase of the gait. In any given cycle, the figures would be consolidated in such a way that the heavily lined areas on the floor would be superimposed (figure 2). Note the various angles of the foot and leg.

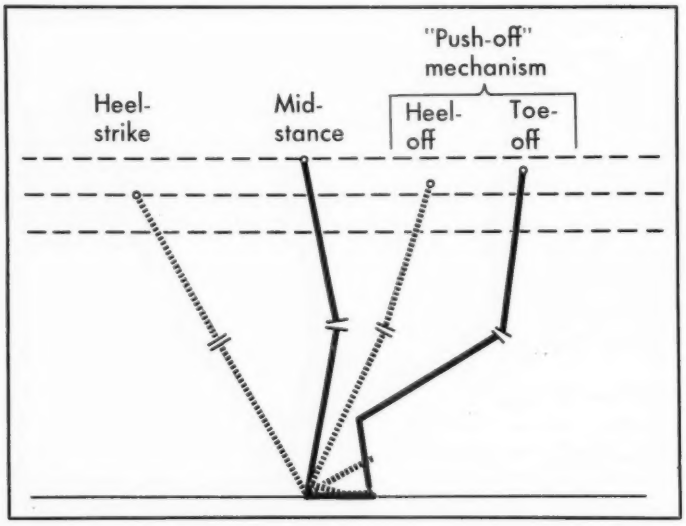

FIGURE 2. Schematic representation of the stance phase. Note the angles of the knee and of the foot and leg in the various components of the stance phase.

Heel-strike is the onset of the stance phase. The leg has come forward through the swing phase and the heel is implanted firmly on the floor or ground. At this precise moment, the knee normally is fully extended and the foot forms an angle of 90 degrees with the leg. Plantar flexion begins to occur at heel-strike.

Immediately after heel-strike, the knee begins to flex and reaches an angle of 20 degrees at midstance. The pelvis then is directly over the foot, the ankle is slightly dorsiflexed, and the pelvis is rotated about the weight-bearing hip in the frontal plane, which allows the non-weight-bearing side of the pelvis to drop. Since the center of gravity of the body ordinarily would tend to be raised quite high at the time of midstance, this dropping of the pelvis has the effect of leveling off the path of the body and thus conserves energy.[1] The

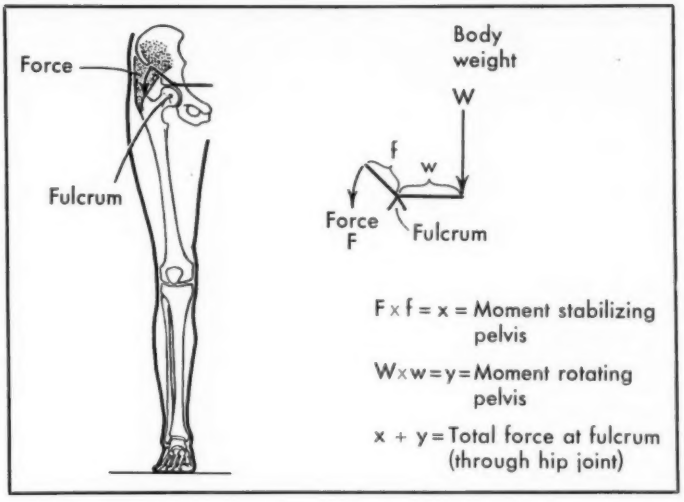

FIGURE 3. Vital elements (force and fulcrum) of function of the hip joint.
y = moment of force tending to rotate the lever system (the pelvis) downward.
x = moment of force counteracting y and tending to stabilize the pelvis.
The length of the lever arm (w) is decreased when the patient sways (lurches) over the hip, thus decreasing y and the sum of x and y. The total force passing through the hip joint is thereby decreased.

muscles that are responsible for this leveling-off action are the abductor muscles of the hip (gluteus medius and gluteus minimus). Since these muscles must work within an intact structural system, the vital elements of hip function in normal gait can be thought of as *force* (normal action of the gluteal muscles) and *fulcrum* (intact femoral head, neck and acetabulum, and a normal relationship between the femoral head and the acetabulum) (figure 3).

After the pelvis moves ahead of the weight-bearing foot, the heel begins to rise off the floor (heel-off). Since there is still about 15 to 20 degrees of dorsiflexion at the ankle at this time, the calf muscles are, in a sense, "cocked" for a short but powerful thrust from this position to 20 degrees of plantar flexion at the end of the heel-off period (figures 1 and 2). Actually, in a slow gait, there may not be any plantar flexion at the ankle, since it is only necessary for the calf muscles to contract and hold the foot-leg angle at 90 degrees. This "riding-over" the lengthened lever of the foot-leg complex and the possible addition of a short, powerful thrust into plantar flexion constitute what is commonly called the push-off mechanism (figure 2). Almost simultaneously with heel-off and consequent push-off, the knee extends for a brief moment and thus gives the push-off mechanism a rigid if not an actively contributing member against which to push.

In toe-off, the final component of the stance phase, the knee begins its terminal flexion as the toe leaves the floor.

The swing phase—This phase of the cycle begins at toe-off and ends with heel-strike. It is merely the swinging of the extremity in preparation for another phase of weight bearing. It requires active function of the flexor muscles of the thigh to pull the thigh forward. This rapid propulsion of the thigh whips the shank forward with minimal muscular activity except that which checks this passive swinging of the shank. The quadriceps femoris muscle checks the terminal flexion of the knee after toe-off, and the hamstring muscles then brake the whipping of the leg forward into complete extension. As a result, these motions are smooth and controlled. Since the non-weight-bearing side of the pelvis drops slightly, the timing and extent of flexion of the knee must be such that the foot, which now forms an angle of about 90 degrees with the leg, can be cleared from the floor as the extremity swings through beneath the pelvis.

Common Deviations From the Normal Gait

Deviations during the stance phase—As plantar flexion begins to occur after heel-

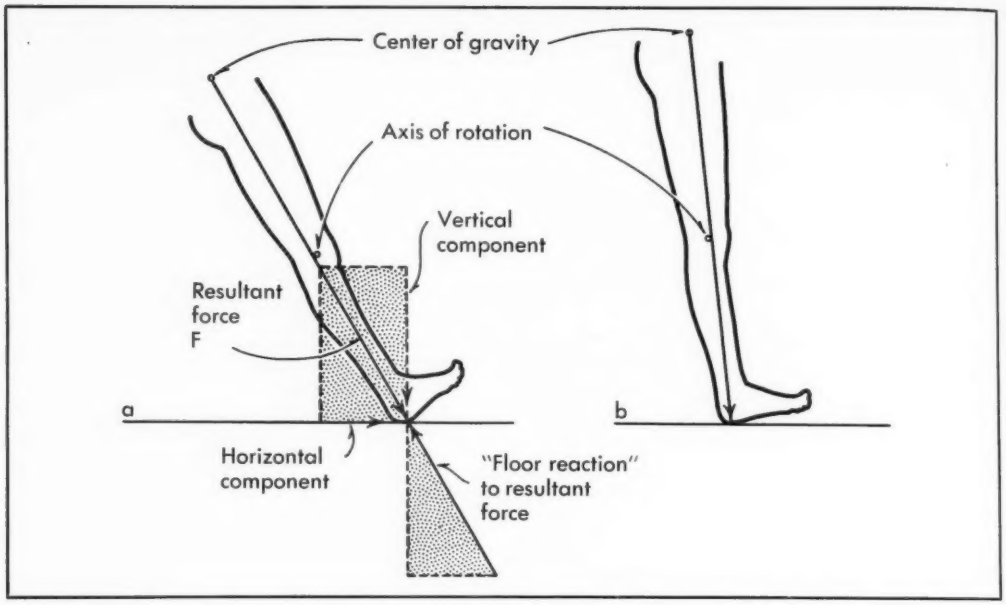

FIGURE 4. Forces involved when the heel strikes the floor (heel-strike).

a. When one takes a long stride, the floor reaction to the resultant force passes behind the axis of rotation of the knee. This causes buckling.

b. When one takes a short stride or leans forward, the line of force can pass through or actually slightly ahead of the axis of rotation of the knee joint and thus create a stable situation.

strike, the foot has a tendency to strike the floor with a distinct slap unless the muscles that cause dorsiflexion are strong enough to check this slapping action. However, this slapping cannot occur unless the muscles that cause dorsiflexion are strong enough to hold the foot at a right angle with the leg in the swing phase.

Immediately after heel-strike, as the knee begins to flex and is bearing weight at the same time, a weak quadriceps muscle may not be able to support the patient's weight. He may have to substitute for this lack of strength of the quadriceps muscle by taking very short strides or by forcing the knee into extension or hyperextension. By taking very short strides, a patient without any quadriceps power whatsoever may be able to walk, since he never allows the weight line, that is, the resultant line of force passing from the center of gravity to the floor (figure 4a and b), to fall behind the axis of rotation of his knee, and he thus maintains stability of the knee throughout the stance phase.

With a very forceful thrust of the gluteus maximus muscle, the patient can extend his thigh so powerfully that the knee is forced to remain completely extended or hyperextended, which is a stable position. He also can force extension of the thigh and thus stabilize the knee by pushing backward on the anterior surface of the thigh with his hand. It should be emphasized that abnormalities of gait due to instability of the knee occur early in the stance phase, that is, just after heel-strike. After that, as the line of force from the center of gravity to the floor begins to pass anterior to the axis of rotation of the knee, the joint is stable because it tends to remain in extension (figure 4b).

Marked deviation in the frontal plane may occur when the requisites of proper function of the hip, namely, force and fulcrum, are not fulfilled. If these are deficient, the pelvis can-

not be stabilized, and its nonweight-bearing side tends to drop abnormally low. The trunk then must sway to the weight-bearing side to maintain balance as well as to prevent to some extent the marked dropping of the opposite side of the pelvis. The swinging through of the nonweight-bearing extremity is thereby facilitated. This combination of events produces the so-called lurching gait.

As one would suspect, the inability of the patient to bring the heel off the floor is due to a lack of adequate contraction of the calf muscles. In order for the heel to rise off the floor, the calf muscles must contract strongly to produce slight plantar flexion or at least hold the foot fixed at an angle of 90 degrees with the leg. Lack of this heel-off component of the stance phase is commonly designated as a lack of push-off. In a case of this type of limp, the patient picks his foot off the floor as a unit instead of raising the heel first, and the heel does not leave the floor until weight is being borne solidly by the other foot.

When weight bearing is painful, the patient will shorten the period of weight bearing. This is the basis of the *antalgic gait*. The degree of shortening of the stance phase will be related to the severity of the pain, but the fundamental deviation in cases of antalgic gait is a change in the timing of the cycle so that the stance phase is relatively brief.

Deviations during the swing phase—The major deviations that occur during the swing phase are related to the fact that the swinging extremity must clear the floor at a time when the pelvis has dropped slightly, when the opposite knee is flexed, and when the opposite foot is flat on the floor (figure 2). Inability to flex the hip or knee (or both the hip and the knee) or to hold the foot up at an angle of at least 90 degrees with the leg will tend to make the swinging extremity relatively too long, and the patient will have to accommodate to this situation in order to prevent the toes or foot from striking the floor as the leg swings through.

Raising ("hiking") the pelvis is a common way to accommodate for a stiff hip or knee in the swing phase. The patient raises the pelvis on the side of the swinging extremity with the lateral muscles of the trunk and by extra effort of the abductor muscles on the weight-bearing side. He also may actually sway to the weight-bearing side to help raise the pelvis. This lifts the stiff extremity and helps to clear the foot from the floor.

To accommodate for a knee that is stiff in extension, the patient usually will circumduct the leg in order to swing it through. If the knee is stiff in extension and plantar flexion is present, the compensatory mechanisms of raising the pelvis and circumducting the leg may both be used. If the muscles that cause dorsiflexion are unable to hold the foot at an angle of 90 degrees with the leg in the swing phase, this inability can be compensated for by raising the knee higher than usual and thus keeping the dangling foot off the floor in the so-called steppage gait. The examiner may have a tendency to detect the compensatory maneuvers, that is, the circumduction of the leg and the raising of the knee, rather than the basic disturbance in the gait.[2]

Abnormalities of gait caused by marked limitation of motion often can be detected in either the stance phase or the swing phase. Fixed deformities also may be detected in both of these phases, but abnormalities of gait that are due to neurologic disease and result in ataxia and athetosis may defy analysis.

Unequal length of the legs is difficult to detect unless there is a considerable difference. In a case in which there is a marked difference in the length of the two legs, it usually is obvious on inspection. The patient has two problems: (1) He must swing the long leg through, and (2) he then must "get down" to the short leg at heel-strike. Both of these difficulties are met by one major compensatory maneuver, that is, flexion of the knee of the longer leg. This allows the longer leg to swing through when weight is borne on the shorter leg, and it maintains the body at a reasonably low level during the stance phase on the side of the longer leg.

Common Causes of Limp

After one has detected the nature and site of an abnormality of gait, certain common etiologic factors should be considered. A good

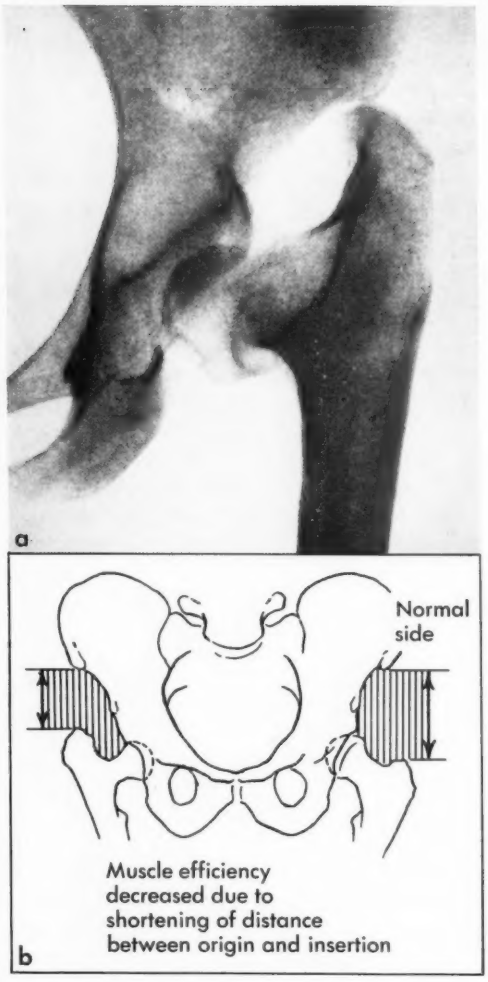

FIGURE 5. a. Roentgenogram of congenital coxa vara.

(From SHANDS, A. R., JR. and RANEY, R. B.: Handbook of Orthopaedic Surgery. Ed. 5. St. Louis, C. V. Mosby Company, 1957.)

b. Schematic representation of the mechanical abnormality responsible for the lurch seen in cases of congenital coxa vara.

history and a careful physical examination are necessary to complete the clinical picture and to establish a correct diagnosis.

The so-called foot slap and steppage gait are manifestations of the same problem, that is, weakness or absence of function of the muscles that cause dorsiflexion. Poliomyelitis is a common cause of such weakness, and is characteristically associated with a spotty distribution of muscle paresis or paralysis elsewhere. Peroneal palsy and consequent foot drop can be caused by trauma, such as local pressure; however, when the foot drop is bilateral, the possible presence of general disease such as plumbism or Charcot-Marie-Tooth disease should be considered. The child with this gait frequently stumbles or trips on small objects. Weakness or absence of function of the quadriceps muscle most often is due to poliomyelitis, but minimal weakness, that is, weakness that is noticeable only when the patient is going up or down inclines or stairs, may be due to chronic disease of the knee.

The lurching gait of inadequate function of the hip joint results from a lack of either of the two requisites of hip mechanics, namely, force or fulcrum. If the former is lacking, as it is in cases of paralysis of the gluteus medius and gluteus minimus muscles, poliomyelitis is the most frequent cause. Loss of efficient function of these hip abductor and pelvic stabilizing muscles also can be caused by a decrease in their length. This occurs in any varus deformity at the hip, for example, congenital coxa vara (figure 5 a and b). This is a developmental abnormality that is characterized by a painless limp which usually is not recognized before the child is four years old.

Slipped capital femoral epiphysis, a disease that occurs about the age of puberty, is associated with a lack of proper relation between the greater trochanter and the iliac crest because of the slip at the epiphyseal plate area (figure 6). External rotation of the limb is a fixed deformity which also is present in cases of slipped capital femoral epiphysis, and it is best seen in the swing phase. The lurch in this disease is also due to pain. When the hip is painful, the patient will place the center of gravity as close to the side of the affected hip as possible during weight bearing, because this will lessen the force necessary to stabilize the pelvis and thus will lessen the total force passing through the painful hip (figure 3). This coxalgic gait is seen in most cases of painful weight-bearing conditions involving the hip joint, and it also includes a short stance phase.

Legg-Calvé-Perthes disease occurs chiefly in boys between 4 and 10 years of age, and it typically results in the coxalgic gait. As a result of the limitation of motion which occurs in this disease, the gait may have a stiff-hip element, but this is difficult to detect unless the child is examined while he is wearing a minimal amount of clothing. It should be remembered that hip pain is frequently referred to the knee in this age group.

The classic example of loss of fulcrum in childhood is congenital dislocation of the hip. In cases of this anomaly, the child walks with a distinct lurch. The normal hip mechanism is completely deranged by the gross instability of the free-floating head of the femur (figure 7). When the anomaly is bilateral, the well-known waddle results. It is hoped that most instances of congenital dislocation of the hip are now being recognized before weight bearing is begun, and that limping due to this anomaly is disappearing from the scene.

The so-called calcaneal gait, or one characterized by a lack of push-off, is often due to weakness of the calf muscles after poliomyelitis. In many cases, the calf muscles will be weak and atrophied after prolonged disuse, as after an injury of the extremity or even after rest in bed as a result of systemic disease.[2] In the latter instance, of course, the loss of heel-off will be bilateral and will not be detected so quickly. Support of the entire weight of the body on the rigid lever of the foot is impossible in many cases of painful conditions of that structure. The heel does not come off the floor, and a calcaneal gait results. This will be seen in cases of trauma as well as in cases of painful flatfoot. It should be noted that the patient will walk with a typical antalgic gait and that the stance phase will be shortened. It is only when the patient is forced to take long strides that the calcaneal element appears.

Foot strain causes an intermittent antalgic limp which is worse at the end of the day.[2] The pain occurs in the calf, not in the foot, and the simple antalgic gait results.

The antalgic gait may occur with any painful condition of a lower extremity, and it is characterized by a short stance phase. This gait is well demonstrated by the simple tack-in-shoe syndrome. If this gait is caused by disease of the hip joint, it will be modified by a lurch; if it is caused by an acutely painful knee, the knee usually will be held in more than normal flexion throughout the gait cycle. If the underlying factor is a painful foot, a calcaneal element will become evident when the stride is increased. It is most important that the possibility of trauma be kept in mind. A minor fracture often will cause a limp in children. The guilt or embarrassment of even intelligent parents often makes it difficult for them to admit their child has been injured.

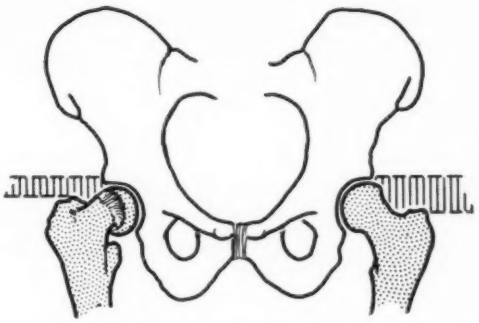

FIGURE 6. Schematic representation of the abnormal mechanics in cases of slipped capital femoral epiphysis. Note the relatively high-riding greater trochanter. The prominent lesser trochanter reveals the external-rotation deformity which also is present.

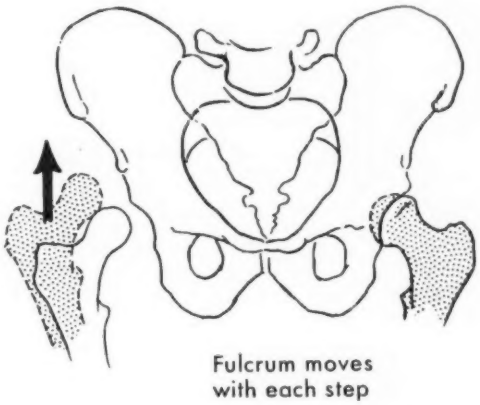

FIGURE 7. Schematic representation of loss of fulcrum, which explains the inability of a patient with a dislocated hip to stabilize the pelvis.

The gait in cases of severe spastic hemiplegia is typical of the circumduction (and sometimes pelvic "hike") that is required to bring a relatively long extremity through the swing phase. The extremity is long because of the exaggerated stretch reflex which causes the postural or antigravity muscles to keep the knee in extension and the foot in plantar flexion.[3]

Toeing-in deformities may be noted in both stance and swing phases. Toeing-in can be caused by adduction of the forefoot, or by clubfoot, internal rotation of the tibia, or exaggerated anteversion of the femur. These conditions have a highly variable prognosis, and they must be diagnosed accurately.

A spastic gait must be recognized. However, the spasticity may not be marked or it may be symmetric. As a result, it may not be detected readily by inspection. One must be careful to think of this gait, to observe carefully the motion of both the upper and lower extremities, and to detect a generally stiff "feel" to the gait. The unsteady broad-based gait of Friedreich's ataxia and the bizarre gait of athetosis occasionally may be seen. These are the results of pathologic conditions of the brain.

Comment

In children, the pattern of locomotion is variable and irregular, and it does not become stable until approximately the seventh year.[1] If the gait of a child of less than seven years has a regularly repeated pattern, the child may be considered to have a limp. Children of this age tend to propel themselves along anything but a straight line. They may skip, hop, jump or run, progressing forward, backward or to the side, but seldom with a steadily repeated pattern for any length of time. This does not mean that the normal mechanisms and their deviations cannot be seen and used to diagnose a limp after the pattern of locomotion becomes fixed. It is this unexpected regularity of the gait, plus a certain asymmetry, that most often catches the eye of the parents and causes them to bring the child to a physician.

If a parent insists that a child has a gait abnormality and if the abnormality is not immediately apparent at the time of examination, it may be helpful to have the child walk rapidly. Increasing the stride sometimes will magnify a minimal deviation in the gait.

In trying to determine the cause of a limp, trauma always should be considered first. The possible presence of trauma should be assiduously ruled out by roentgenographic examination.

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Health Department Nutrition Services and the Physician

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THE practicing physician is the logical authority to whom many persons turn for an answer to the question What shall I have to eat? His office is a center for educating individuals to adopt modern health practices and to reject harmful ones. Nutrition is a large and vital part of medicine and health education. In caring for the pregnant woman, the physician is concerned with the nutrition of the fetus through the mother. He promotes normal growth and development by teaching the mother what is best to feed her children, and he offers adults and the aged the hope of healthier and happier years through sane eating. He is deeply involved with nutrition and diet in any thorough diagnostic and therapeutic procedure, and he considers diet an essential in helping the patient do his part in the management of such conditions as diabetes, heart disease, cirrhosis, nephritis, anemia, fatness and leanness, colitis, peptic ulcer, or the malabsorption syndrome or any combination of conditions the patient may have.

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What shall we have to eat? is a question as old as man and as basic and personal as where to live and what to wear. The usual reply is, What would you like? The practical possibilities are then discussed. Foods or dishes not liked or inappropriate are disregarded. A choice is made from the foods that are expected to give the most pleasure. Unfortunately, many healthy people make meals an ordeal instead of an enjoyable experience, because they worry too much about whether or not they should eat certain foods. Others tinker with their diets to conform to the latest popular fads or fears. Wives worry about what they should feed their children and their husbands. The ill and the overweight worry about just what the doctor meant when he prescribed a special diet for them.

Instruction in the principles of good nutrition and in the essentials of an adequate diet for the promotion of health is relatively easy and not very time-consuming. Many excellent educational aids are generally available. Diet as an aid in treating disease is quite another matter. Such diets are necessarily restrictive. They may be easily tolerated for a few days in an acute emergency, such as a gastrointestinal upset. However, because of monotony and unsatisfied appetite, restrictive diets present numerous difficulties, especially in treatment of chronic disease. These difficulties are

better appreciated by the physician if he has first tried the diet himself. After deciding on the best diet for his patient, he should then determine what restrictions are humanly and economically possible and acceptable to the patient.

Satisfactory adherence to diet demands unceasing cooperation by the patient and close attention to detail by the physician. The dietary details which promote cooperation include teaching certain basic concepts of nutrition and providing for the nutrient requirements peculiar to the patient's condition, sufficient bodily energy, likes and dislikes, satisfaction in quality and quantity, and simplicity and flexibility (so that some items may be interchanged for variety from day to day).

Some physicians prefer to give dietary instructions and advice themselves; others have their office nurses do so. Most busy practitioners have neither the time to provide as much information as they would like nor the detailed knowledge to answer all the questions asked by the patient during or after dietary instruction. Frequently, educational material on a normal diet or a printed list for a special diet is provided the patient. These answer some questions. However, fitting a prescribed diet into everyday living inevitably raises more questions than can be covered in the best of educational aids. A dearth of questions from a patient on a severely restrictive diet should alert the physician to the possibilities of excessively rigid compliance (often of short duration and followed by indifference) or a preference for the consequences of the disease over the diet. Some patients attempt to interpret dietary instructions themselves because of embarrassment or not wishing to make another office call; thus, they are likely not to consume the intended diet. Many physicians would welcome assistance in helping patients with restrictive diets and in answering the inevitable questions that arise, but they are not aware that such help is available or of where to look for it.

Explaining the reasons for dietary restriction is usually most helpful in enlisting a patient's cooperation. Of even greater importance to the patient in his successful adaptation to a therapeutic regimen is sufficient factual information about foods as they relate to a special diet. The greater the degree to which this information is provided, the more decisions the patient is able to make with confidence in suiting the prescribed diet to his own circumstances and in avoiding unnecessary restrictions. His enjoyment of living is disturbed as little as possible, and he has a sense of participation in improving his health. Time, patience, knowledge of food composition, and understanding of the total living situation are necessary to teach a patient how to follow his diet with some degree of enjoyment and a minimum of inconvenience and expense to himself and his family. These attributes are possessed by the public health nurse.

The following discussion presents an ideal situation in which adequate numbers of well-trained public health nurses, backed by consultant nutritionists, are available in the community. Physicians should make use of their services in such situations, and, where such services are inadequate or do not exist, they might use their influence to promote them.

The Public Health Nurse

The public health nurse is trained and experienced in helping patients follow their physician's orders. Whether she is on the staff of a local health department or a visiting nurse in a voluntary agency, her assistance is available to the practicing physician for his patients. Nursing service from health departments is available to patients regardless of their financial status or the help they may receive from any community agency.

The public health nurse is equipped to offer instruction in therapeutic diets, but, all too often, nursing service is an untapped source for practical dietary assistance.[1]

The public health nurse's personal interest in the patient may make the difference between success and failure in his following a dietary regimen. By supplementing the physician's explanation, she is often able to increase the patient's understanding of the reasons for certain dietary changes. She can help in minimizing the need for different meal preparation by suggesting ways in which a common

table may be shared satisfactorily and economically. In this manner, she may influence favorably the eating habits of the entire family in terms of normal diet and nutrition.

In addition to promoting good nutrition practices in family health service, the public health nurse integrates sound nutrition teaching in her clinic and school health work, in group classes such as those for expectant parents or diabetics, and in her work in migrant labor camps and on Indian reservations. She often has the opportunity to lend support to better school lunch programs and to improvement in feeding practices in nursing and convalescent homes, homes for the aged, day-care centers, child-care institutions, industrial establishments, and institutions of all kinds.

The physician frequently turns to the dietitian for instruction of his hospitalized patients and for assistance in adapting dietary details to home situations. The public health nurse often calls on the community's counterpart to the hospital dietitian, the public health nutritionist, for help with difficult nutrition problems. Usually, consultation between nurse and nutritionist is sufficient. If the patient needs direct help, the nutritionist is available at the physician's request. Consultation between nutritionist and patient is more frequent when the former is part of a team providing direct health services and when she is employed in city or county agencies.

The public health nurse is often responsible for acquainting the community with the services of the nutritionist and for preparing the way for direct consultations between the nutritionist and the hospital administrator or food service supervisor in regard to menu planning and modified diets in hospitals without a qualified dietitian or between the nutritionist and a nursing school faculty in regard to integrating foods and nutrition in the curriculum.

The Public Health Nutritionist

Almost every state health department and a large number of county and city health departments employ one or more public health nutritionists. Services of a state health department nutritionist are generally available to local health departments which do not have staff nutritionists. Of about 400 nutritionists employed by health agencies, some 300 in state and local health departments and visiting nurse associations provide on-the-job education in nutrition for public health nurses and other professional personnel and are available to them and to practicing physicians for consultation. The remaining nutritionists work in voluntary health agencies, the American Red Cross, professional education programs, federal and international agencies, and research institutions.

The minimal preparation required for public health nutritionists to secure competence in the science of nutrition includes academic preparation at both undergraduate and graduate levels. Their undergraduate education, leading to a bachelor's degree, follows the recommendations of the American Dietetic Association. It includes courses in chemistry, physiology, microbiology, normal nutrition, advanced nutrition, nutrition in disease, food selection and preparation, meal planning and service, food service management, educational psychology, and the behavioral sciences.

The graduate program for public health nutritionists leads to a master's degree with emphasis on public health nutrition. It includes advanced study in nutrition and special needs in disease, community organization, social welfare, education, and the behavioral sciences. At least two months' field work in a public health agency is also part of the graduate curriculum.

Most public health nutritionists are members of the American Dietetic Association, such membership being considered by the American Medical Association as necessary for a person to be a qualified dietitian. Many public health nutritionists have completed a dietetic internship, have had several years of hospital experience, and speak the doctor's language. A year's experience in public health or community nutrition is ordinarily a minimal requirement for any nutritionist position above the entrance level.

This training and experience equip the nutritionist with a knowledge of practical nutrition that no other public health specialists

ordinarily possess in as useful detail. An understanding of racial, religious and psychologic factors that influence food habits; a working knowledge of food economics, including costs of food, standards of public assistance, and planning low-cost meals; special competence in the best methods of preparation and service of attractive meals for numbers of people, families and individuals; and a thorough understanding of the principles of diet therapy and their application to individual patients are the attributes of the public health nutritionist. Through these she is able to broaden and enrich the public health nurse's understanding and perspective and to increase her competence in nutritional guidance.

Functions of a Nutrition Unit in a Health Department

The major function of a nutrition unit is to provide an educational program to promote the adoption of modern nutrition practices among the population. The program is directed primarily to professional persons in agencies, organizations and groups who educate or are responsible for promoting health matters. An especially important phase of this program is the in-service education of the professional staff of the health department at levels appropriate to their duties and responsibilities. Nutrition services are emphasized for groups of people most likely to be susceptible to nutritional difficulties, including expectant and nursing mothers, infants and children, adolescents and the aged, those with chronic illness or physical handicaps, and those with limited food budgets or restricted sources of food. Residents of institutions of all kinds depend essentially on the administrative and food service personnel of their institutions for adequate nourishment. Consultation and technical assistance are made available on request, and training programs are developed for all types of institutions.

Providing consultation services on nutrition problems, developments in nutrition research and their practical application, survey and research methodology, and the administration of nutrition aspects of health programs is a necessary supportive service to the educational program. In the most highly developed nutrition units in health departments, there is actual participation in research projects, such as work on the nutritional aspects of atherosclerotic heart disease. The use of good and appropriate nutrition education materials for lay and professional use is promoted, and new materials are developed where none exist.

Many official and voluntary agencies have certain responsibilities directly concerned with or affecting the nutrition of the public. An important function of the nutrition unit in a health department is to develop a coordinated approach to the total problem among these agencies in order to identify unmet needs, minimize duplication, and complement activities so that a truly comprehensive program of nutrition education and of services may be developed.

Summary

A nutrition unit of a health department is an authentic source of information, advice and assistance for all the people served by the department. This discussion gives a detailed account of how such a unit may assist the private patient on a restricted diet at his physician's request. The broad scope of a nutrition unit's responsibilities and functions should suggest that no question or problem, however remote, about foods and nutrition is foreign to the concern of the unit.

The small number of public health nutritionists in any single nutrition unit dictates that their efforts are directed where they can be most effective, with particular reference to improving the nutrition practices of those segments in the population most in need. Because the nutrition unit's work is mainly, although not exclusively, with those whose activities affect the health and welfare of large numbers of people and even of an entire population, the general public and many professional persons are at present exposed only indirectly to the diverse activities of such a unit.

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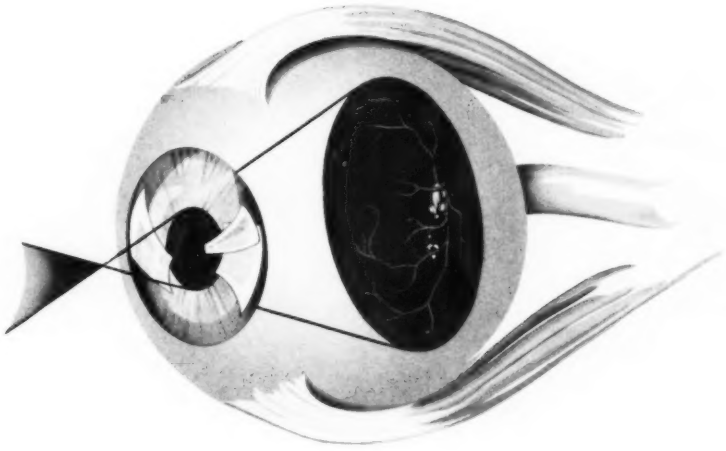
SCIENTIFIC EXHIBIT

The Eye
in Persons Aged 65 and Over



AN INTRODUCTION TO THE PROBLEM

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Adapted from an exhibit presented at the 1960 annual meeting of the American Medical Association, Miami, Florida.

Introduction

With the continued marked increase in the number of senior citizens, many of whom are otherwise well except for poor sight, the preservation and restoration of their vision have become a major ophthalmologic problem.

In studying their ocular status, I chose age 65 as a convenient starting point simply because it seems to be the age most commonly selected for industrial and legal purposes as the time of retirement.

Of the first 5,192 consecutive charts analyzed, 801 (15.5 per cent) were those of persons aged 65 and over. Surprisingly, 83 per cent of this group had vision of 20/50 or better. The chief causes of visual incapacity were cataracts, macular disease, glaucoma, and vascular changes and accidents. In many cases, two or more conditions existed simultaneously. A number of diseases found in younger persons were also seen in the older age group, often in more-advanced stages.

A brief discussion of some of the more important ocular physiologic and pathologic changes found in persons aged 65 and over and some suggested approaches to therapy are offered with the hope of stimulating more attention to this area of ophthalmology.

Senile Ocular Changes

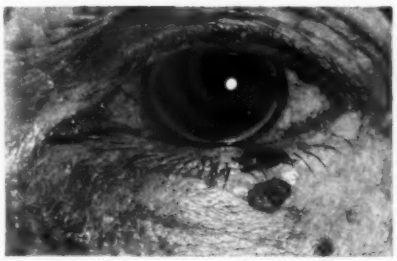
Physiologic changes do not come on suddenly at any one age, and they vary among individuals. A patient's eyes may be older or younger than his chronologic age indicates.

Certain changes are physiologic, as the progressive loss of accommodation, progressive drying and opacification of the lens, progressive depigmentation of the iris, loss of retinal reflexes, etc. Other changes, which may begin earlier in life, although they are not necessarily physiologic even then, tend to assume a more malignant aspect with advancing years. Among this group are the glaucomas, lens opacities, high myopias, vascular changes, and the progressive forms of macular disease.

Early in their course, many of these changes produce so little effect on vision that they frequently are unnoticed by the patients. As the changes progress due to lack of treatment or inadequate treatment, they become increasingly more serious either because therapy will not restore any of the lost vision or because there is no known effective treatment.

Skin and Lids

Thin, pigmented skin; keratosis.
Senile stretching of skin, ptosis, entropion, ectropion.



Warty-pigmented skin. Arcus senilis.

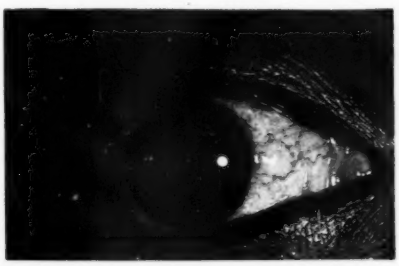
Carcinoma of lid. Note crow's-feet.

Spastic entropion.

Senile stretching.

Conjunctiva

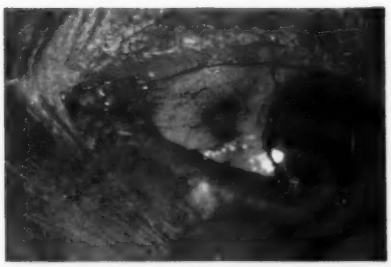
Thin, fragile (hemorrhages), pinguecula, chronic irritations.



Pinguecula.

Sclera

Hyaline scleral plaques, occasionally; scleromalacia perforans, rarely.

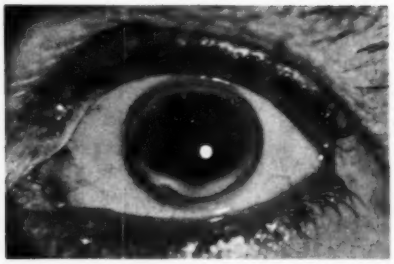


Hyaline scleral plaque.

Cornea

Smoky appearance; arcus senilis; dystrophic changes, especially in endothelium.

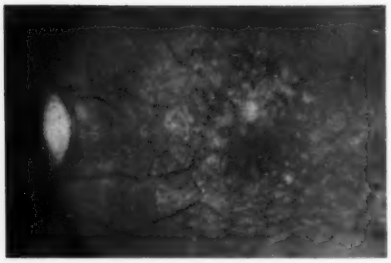
Epithelial and endothelial dystrophy.



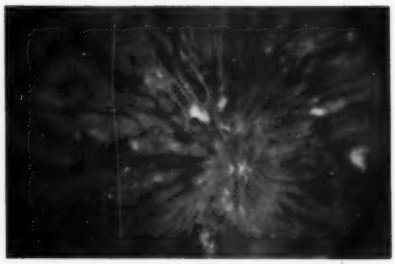
Gutter dystrophy.

Retina

Drying, loss of light reflexes, colloid degeneration, macular degeneration, cystic changes in periphery, vascular changes and accidents.



Colloid degeneration (drusen).



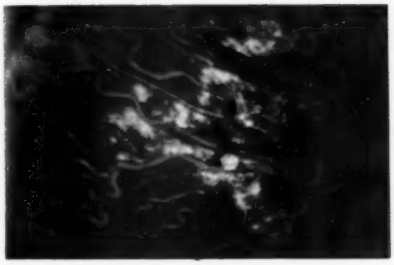
Thrombosis of central retinal vein.

Cystic changes in periphery.

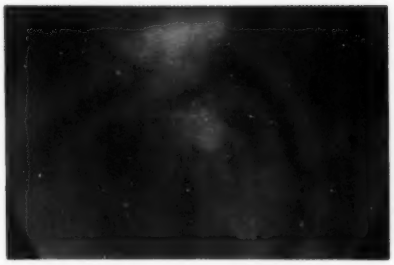
Macular degeneration.

Choroid

Sclerosis of vessels, neoplasms.



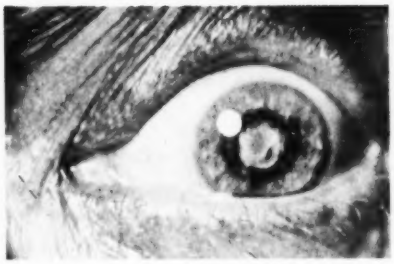
Choroidal sclerosis.



Malignant melanoma of choroid.

Lens

Cataract.



Cataract.

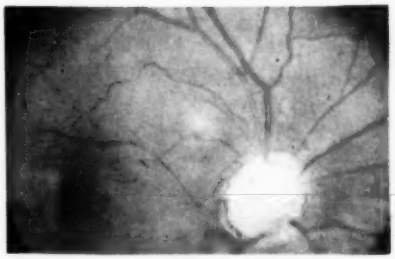
Extraocular Nerves

Transient muscle palsies associated with diabetes, hypertension, cerebrovascular diseases, and neoplasms.

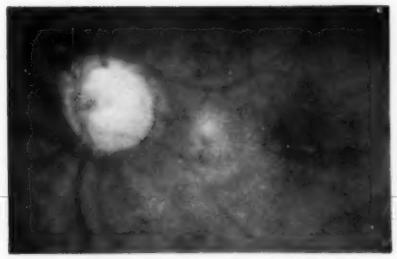
Paralysis of left third cranial nerve.

Optic Nerve

Cavernous atrophy, pseudopapilledema (buried drusen), glaucoma, cerebrovascular accidents and diseases.



Glaucomatous cupping.



Cavernous atrophy.

Vitreous

"Spots before the eyes," a common complaint, usually due to degeneration of the fibrous network of the vitreous, asteroid hyalitis or hemorrhages.

Management

Anything that will improve a patient's health and sense of well-being will tend to improve his visual function and lessen tiring on visual effort. Maintenance of good nutrition, including proper diet, vitamins and sex hormones, may be reflected in improved vision.

We can do a great deal to preserve or improve the visual function of elderly persons even though we do not know the etiology of many of the disabling diseases, the most important of which are cataract, glaucoma and macular and vascular diseases.

Cataracts

When careful refractions no longer give useful vision, surgery is the only answer. Cataract extraction in good hands is a highly successful procedure. If the patient has a fairly good retina and choroid, the results will be most satisfactory. If there is a macular lesion, central vision will be impaired, but can be aided with low-vision aids.

When the cataract is known to be associated with other diseases, such as glaucoma or macular degeneration, the problem is more complicated. The surgeon must attempt to assess the relative disabling status of each of the concurrent diseases and base his approach on his assessment.

Glaucoma

The most important and prevalent of the many forms of this disease are acute, chronic wide-angle, chronic narrow-angle, and secondary glaucomas.

An attack of acute glaucoma is responsive to miotics and carbonic anhydrase inhibitors or intravenous urea, or both. When the first attack has been controlled medically, further attacks can usually be prevented by early surgery.

Chronic wide-angle glaucoma can usually be managed by medical therapy, but may require filtering surgery moderately late in its course. Careful management with miotics, including pilocarpine and BC 48, often effects a response. BC 48 requires less frequent instillations and can be accompanied by the use of certain mydriatics, such as phenylephrine hydrochloride, and the carbonic anhydrase inhibitors when miotic therapy alone does not suffice.

Chronic narrow-angle glaucoma in a sense is a less violent version of acute glaucoma. Further attacks can usually be prevented by early surgery. With repeated attacks, management becomes more difficult. The problem is a highly individual one, depending on the frequency and severity of the attacks, the age and health of the patient, and the therapeutic philosophy of the ophthalmologist. The earlier the age of the patient at onset and the healthier he is, the more that can be accomplished by early surgery. If the patient is aged or infirm, one may temporize treatment, using miotics and carbonic anhydrase inhibitors.

Unfortunately, therapy for the chronic glaucomas does not return lost visual fields or vision. Therefore, early diagnosis is most important. Since the patient may not be aware of the disease in its early stages, diagnosis demands vigilance by ophthalmologists during routine refractions, intensive educational campaigns, and tonometry during routine physical examinations by physicians who are competent in its use and interpretation.

Secondary glaucoma is secondary to other eye diseases, intraocular neoplasms, trauma, etc. The most common cause in elderly persons is uveitis, which responds to adequate systemic and topical steroid therapy. The accompanying secondary glaucoma tends to respond to the same medication plus carbonic anhydrase inhibitors. If it does not, surgery is indicated.

Macular Degeneration and Diseases

Although macular degeneration and diseases are progressive, they should not be regarded as hopeless. In the case of inflammatory disease, systemic and subconjunctival administration of adrenocortical steroids will be beneficial. When given early and intensively, they will mitigate resultant macular scarring. I have also used this treatment successfully in many macular conditions of unknown origin, which have followed lens extractions.

There is no known effective therapy for senile macular degeneration per se. The accompanying edema can often be relieved by systemic and subconjunctival administration of adrenocortical steroids, with visual improvement.

Vascular Diseases and Accidents

Other important causes of visual disability are vascular diseases and accidents, which are often part of a systemic condition. Fortunately, the whole subject of cardiovascular disease is under intensive investigation, with various anticoagulant and thrombolytic agents on trial. Anything that will mitigate general vascular disease can be expected to improve the secondary ocular conditions as well.

In some cases of large retinal hemorrhages near the macula or in other vital areas, I have found courses of heparin sodium markedly beneficial. Anticoagulant therapy has many advocates in treatment of retinal venous thromboses. Evidence shows that some retinal vascular accidents, especially those involving veins, are on an inflammatory basis and will respond to adequate systemic steroid therapy. Certainly this merits at least a short trial in venous occlusions, simultaneously with anticoagulant or thrombolytic therapy. The role of systemic steroid therapy in preventing visual loss in temporal arteritis has been well documented. A medical regimen which often includes the chlorothiazides may relieve hypertensive retinopathy.

Miscellaneous Conditions

Extraocular muscle palsies, which occur most frequently in patients having diabetes or hypertension, will usually clear in six weeks or more. To facilitate the process, I give injections of vitamin B_{12}.

"Sandy" sensations, tearing, and other conjunctivitides of the aged may be treated with topical decongestants and steroids.

A high percentage of persons who lack useful near vision can be aided by a variety of low-vision aids. Often the addition of a small amount of magnification either as a hand magnifier or incorporated into spectacles has made life more comfortable.

Comment

It is important to realize that loss of central vision may not be catastrophic, since this means loss only of ability to read and to recognize detail. If the peripheral vision is good, the individual can still get around well and may be able to read with magnification. If central vision is intact and the peripheral field is lost, the individual can read but cannot navigate with ease. All things being equal, it is more important to be able to get about on one's own than to be able to read. Although, paradoxically enough, reading is more important to the sedentary aged person than to the more active young person.

SYMPOSIUM

Diabetes Today: Medical and Surgical

THADDEUS S. DANOWSKI,[1] STEFAN S. FAJANS[2] AND LELAND S. McKITTRICK[3]

Methods and criteria used in diagnosing and controlling diabetes, brittle diabetes, diabetic coma, circulatory problems and orally administered hypoglycemic agents are among the various aspects of diabetes considered in this discussion.

The authors also differentiate between prediabetes and latent diabetes, pointing out that the former is often undiagnosed until diabetes develops, while laboratory procedures will demonstrate the latter.

Patients should be examined for latent diabetes before surgery, as this condition may influence the type of operation, the anesthetic employed, and the time lapse before surgery is performed.

THADDEUS S. DANOWSKI

DR. THADDEUS S. DANOWSKI (Moderator): Diabetes has seldom been described in precise terms in the literature. This disease is a disturbance of the total metabolism of the body, i.e., of carbohydrate, fat and protein, which is most readily detected by an inability to dispose of carbohydrate loads at a normal rate. The disturbance involves all foodstuffs, but it is most readily detected by the presence of hyperglycemia. It may be characterized by inadequate proteogenesis with negative balances of nitrogen and by lipid disturbances with excessive ketone body production, increases in nonesterified fatty acids, and impairment of lipogenesis.

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Latent Diabetes and Prediabetes

Dr. Fajans, how would you define latent diabetes and prediabetes?

DR. STEFAN S. FAJANS: Dr. Danowski has described the abnormalities that may exist in diabetes mellitus. A patient who manifests such gross abnormality of metabolism, including considerable glycosuria, would be likely to present the usual classic symptoms referable to the disease, namely, polyuria, poly-

STEFAN S. FAJANS

LELAND S. MCKITTRICK

dipsia, weight loss and polyphagia. In latent diabetes, there are no symptoms referable to the disease, but the condition may be diagnosed by laboratory procedures. A patient with latent diabetes may have fasting hyperglycemia but have no symptoms. On the other hand, the fasting blood sugar level actually may be within the normal range. Then, the earliest detectable abnormality is undue hyperglycemia after eating or during a glucose tolerance test.

In differentiating between prediabetes and latent diabetes, we first consider that diabetes is a hereditary disease. Individuals in whom diabetes mellitus eventually will develop are born with a predisposition or susceptibility to the disease. Prediabetes, then, is defined as a state which exists from birth until the time that a definite diagnosis of diabetes can be established by presently accepted criteria. By this definition, prediabetes is not synonymous with latent or asymptomatic diabetes mellitus.

DR. DANOWSKI: Where do you look for prediabetes, Dr. Fajans?

DR. FAJANS: I look for prediabetes first of all in close relatives of diabetic patients, including their parents, siblings and children. There also are certain clinical manifestations which we associate with the prediabetic state. One group of such manifestations is related to pregnancy. For example, a woman who gives birth to a 10 lb. baby has an 85 per cent chance of being or becoming a diabetic. If she does not already have diabetes, she would be classified as a prediabetic. If a woman gives birth to a 13 lb. baby, the chances are increased to 95 per cent. Unexplained spontaneous abortion or giving birth to a child who dies shortly thereafter, particularly if the child is edematous, is also a manifestation of prediabetes. In addition, renal glycosuria in a nonpregnant person may be a sign of the prediabetic state.

DR. DANOWSKI: Obesity and the development of carbohydrate intolerance in pregnancy should be added to the prediabetic manifestations.

DR. FAJANS: I would not classify obesity per se as a prediabetic state. Obesity may bring out diabetes in a prediabetic person, but it will not do so in a person without a predisposition to diabetes.

DR. DANOWSKI: It is possible that the husband of a woman who gives birth to a large baby may be a prediabetic, although this has not been clearly established. Prediabetes is a mysterious state. We can speak of it only as a possibility, since we cannot really make a diagnosis of prediabetes until diabetes actually develops.

DR. FAJANS: I would like to differ with the opinion that prediabetes cannot be diagnosed until diabetes appears. We have been using a cortisone-glucose tolerance test, and we believe positive responses to this test indicate a prediabetic state even though results of the standard glucose tolerance test are negative. We have followed over 100 such cases and have found that diabetes has developed in 25 per cent and probable diabetes in another 10 per cent of those with positive responses to the cortisone-glucose tolerance test. Diabetes has developed in only 2 per cent of those who had negative responses. Thus, it may be possible to recognize the prediabetic state.

DR. DANOWSKI: This may be quibbling with words, but I would say that you are identifying latent diabetes with this test. Diabetic-type changes in the results of the glucose tolerance test will be seen in anyone given pharmacologic dosages of steroids over a period of time. Undue blood sugar increases will occur during glucose tolerance tests. This increased hyperglycemia arises predominantly from an increased glucose load created by the steroids and in part from a blockade of insulin action.

What you are describing, of course, is a test based on a precise amount of steroid which in nonsusceptible individuals does not produce an undue hyperglycemia. However, in susceptible persons, whom you call prediabetics, an unduly hyperglycemic curve results.

Dr. McKittrick, how extensive should be the examination for latent diabetes before major surgery is performed?

DR. LELAND S. MCKITTRICK: We do a routine urinalysis, and if there is some reason to suspect the presence of latent diabetes, we do tests of fasting blood sugar and of blood sugar one hour after a meal. If the results are negative, we feel this is sufficient.

DR. DANOWSKI: Have you ever seen a patient in whom diabetes developed during a surgical illness and who recovered from the diabetes? I recall a patient in whom diabetic coma developed during hospitalization for a perforated peptic ulcer. He recovered with treatment, and, on discharge from the hospital, he had no evidence of diabetes.

DR. MCKITTRICK: I have never seen such a case. Apparently, the diabetes manifested itself under the stress of illness and a major surgical procedure. When the illness had resolved, the diabetes, for all practical purposes, disappeared.

DR. DANOWSKI: Do you agree, Dr. Fajans, that we would still consider that this patient has latent diabetes and that diabetes could again develop under adverse conditions?

DR. FAJANS: I would certainly think so.

Surgery in the Diabetic

DR. MCKITTRICK: I would like to consider further the question of the examination for diabetes before surgery. I first would like to state that I believe that the real surgical emergencies are few and far between. More lives are lost through so-called emergency surgery in the middle of the night than are saved by it, because too little is known about the patient. Not many conditions warrant this type of treatment.

I also want to point out that any patient in the emergency ward usually has a needle placed in his vein for an intravenous feeding of some 5 per cent glucose in water or saline. A certain amount of this is going to come out in the urine; thus, the first urinalysis may show some sugar. The problem is to determine whether or not these patients are really diabetics. In many of these cases, I have been prone to do an emergency test for blood sugar, or to do one the following day, before any glucose is given. With these glucose infusions, I think we can overlook a diabetic and really get into difficulty.

DR. DANOWSKI: What effect will the presence of diabetes have on the patient as an operative risk?

DR. MCKITTRICK: I think it makes a difference. In evaluating such a patient, I first consider that he presumably has had diabetes for some time. It has been my impression that if a person has had diabetes over a period of years, the disease probably has done something to him; he is a little bit different from another person of his own age who otherwise is comparable. So, I am more careful in examining his cardiovascular status, urinary tract, peripheral circulation, etc., because this patient may not be quite as good an operative risk as a patient who does not have diabetes.

Then, I consider that because he has diabetes he has a metabolic disturbance which is going to be affected by whatever I do to him and that this must be controlled. What I do to that individual, whether or not I advise operation, and the type of operation I carry out will be influenced by my evaluation of these factors. If I find on more careful investigation that the patient's kidneys are affected, that he has a little retinopathy, or that he does not have any pulses in his pedal arteries, I consider him with a great deal of apprehension.

In some instances, when I have been performing amputations on such patients, I have modified the kind of amputation to reduce the possibility of postoperative complications. So, the selection of the type of operation and the anesthetic and the determination of the time lapse before the operation is performed depend on these factors.

DR. DANOWSKI: Of course, you are referring to the well-known fact that people who have had diabetes for a number of years generally

have more disease of all their blood vessels than does the aging population as a whole. This can involve the peripheral arteries and the arteries of the brain and heart. In addition, when diabetes develops in a woman, she loses her relative freedom from vascular disease. Thus, myocardial infarctions occur in the female diabetic about as often as they do in the male nondiabetic. Retinopathy also may be present in a patient with diabetes of long duration. Changes in the kidney are usually manifested as intercapillary glomerulosclerosis and may result in the Kimmelstiel-Wilson syndrome; however, other pathologic conditions also may be present in the kidneys. Some physicians use the term "nephropathy" for all urinary abnormalities in the diabetic; however, since this term indicates merely disease of the kidneys, it should be used only when the pathogenesis is unknown.

Dr. McKittrick, do you use oscillometry to determine the state of circulation?

DR. MCKITTRICK: Although it probably would be very helpful, I have never used oscillometry. I believe that we can learn more from what we can see, hear and feel and from the occasional use of the blood pressure cuff than from trying to interpret a complicated mechanism such as the oscillometer. We have found it helpful in evaluating primary but not collateral circulation.

DR. DANOWSKI: We use the oscillometric index, but I think it is a very crude apparatus, and it is very difficult to distinguish gradations of change. It is not a precise index that absolves you from using the various procedures that Dr. McKittrick mentioned.

Diagnosis

Dr. Fajans, you have already pointed out that the fasting blood sugar may be perfectly normal in a diabetic person. How may we unequivocally establish the presence or the absence of diabetes?

DR. FAJANS: Use of the word "unequivocally" makes this difficult to answer, because physicians do not use identical criteria for interpreting a glucose tolerance test. We use the following methods and criteria. First, we prescribe a high-carbohydrate diet for three days before performing the glucose tolerance test. Secondly, the blood analyses are made on venous blood. Our criteria of abnormality are a peak blood sugar level (occurring usually at one hour) of 160 mg. per cent or above and a two hour level of 120 mg. per cent or above. To eliminate the occasional rebound curve, where blood sugar falls to normal levels by one and one-half hours and then rebounds back to 120 mg. per cent or above by two hours, we require the blood sugar level at one and one-half hours to be 140 mg. per cent. If the two hour level falls between 110 and 120 mg. per cent but the peak blood sugar level at one hour is still 160 mg. per cent or above, we call this "probable diabetes." These figures apply to a true method of determining blood sugar, such as the Somogyi-Nelson technic. If the older Folin-Wu technic is used, approximately 20 mg. per cent must be added to these figures.

These criteria apply only to the otherwise healthy, ambulatory individual. They do not apply to the acutely or chronically ill patient who is immobilized in bed for long periods. We have confidence in these criteria because, when we applied them to 127 healthy subjects without a family history of diabetes mellitus, we found that the results of the glucose tolerance test showed definite diabetes in only one and probable diabetes in only one other. When we applied the same criteria to healthy relatives of diabetic individuals, we found an incidence of 19 per cent of latent diabetes and another 4 per cent of probable diabetes. Furthermore, follow-up of persons with mildly abnormal results of the glucose tolerance tests often shows subsequent development of unquestionable diabetes.

DR. DANOWSKI: I agree with these criteria. I think an otherwise healthy person whose peak blood sugar level is above 160 mg. per cent and whose two hour level is above 120 mg. per cent is either diabetic or very close to it. Of course, if the blood sugar is 121 mg. per cent at two hours, I repeat the test.

Dr. Fajans, what do you think of performing glucose tolerance tests without three days of high-carbohydrate feeding?

DR. FAJANS: I would say that it probably

makes little difference if the patient has not been starving or on a reducing diet. If you are referring to the recent studies from Boston showing that limiting carbohydrate for three or six days does not matter, I would agree. We are worried about the prolonged deprivation of carbohydrate and the reproducibility of the glucose tolerance test. If in the same patient you compare results of the glucose tolerance test following a 150 gm. carbohydrate diet with those done following a 300 gm. carbohydrate diet, you will find that the curves are not identical. Those performed after the 150 gm. carbohydrate diet show higher blood sugar values; they still are within normal limits but are higher than those done after the 300 gm. carbohydrate diet.

We like to compare results of glucose tolerance tests done this year with those done last year and five years ago in patients with a family history of diabetes. This is why we believe that the high-carbohydrate diet is important if one wants to compare results in the same patient over a span of years.

DR. DANOWSKI: For ordinary purposes, if results of a glucose tolerance test without a three day high-carbohydrate diet are normal, you have your answer. If results are abnormal, you can repeat the test after giving a high-carbohydrate diet.

Postoperative Management of the Diabetic

Dr. Fajans, how do you regulate a diabetic patient who has recovered from a surgical procedure?

DR. FAJANS: We use urine testing, but not exclusively. Every time the patient comes to our offices at the hospital, we determine the fasting blood sugar level. We use this in preference to the postprandial blood sugar determination, so that we will know the patient's metabolic state after an overnight fast. For example, a patient who usually has fasting hyperglycemia before initiation of therapy not only cannot dispose of a carbohydrate load but also cannot even utilize the amount of glucose that is produced by the liver from glycogenolysis and gluconeogenesis in the fasting state. When we get the fasting blood sugar to normal levels by any means whatever, we know that we have corrected a very fundamental abnormality. Of course, our ideal of control is not only fasting normoglycemia but also the prevention of postprandial hyperglycemia and glycosuria. We do not perform many postprandial blood sugar determinations for our day-to-day control; we rely on the absence or presence of glycosuria to evaluate postprandial hyperglycemia. This is true only when we have evidence that the patient has a reasonably normal renal threshold.

DR. DANOWSKI: These are good points, Dr. Fajans; however, I believe that if we rely too heavily on the blood sugar levels, we are setting up an entirely false philosophy of treatment in the patient's mind and in ours. Just consider the fact that 99 per cent of the time we are not treating the diabetes; it is being treated by the patient or his family. Therefore, I firmly believe the chief emphasis in regulation insofar as the patient is concerned should be the daily urine test and not the monthly or bimonthly sugar level. Otherwise, patients tend to go into training for two or three days and watch their diet so that the urine sugar is zero and the blood sugar is normal at the time of the visit to the physician. We therefore agree that the blood sugar determinations should only supplement the regular urine testing in a program of diabetic regulation.

If the urine and blood tests reveal undue hyperglycemia while the patient is on a diet, we use insulin therapy. In general, one or two types of insulin are effective and sufficient. We like to use a mixture of NPH and regular insulin, and 90 to 95 per cent of our patients who require insulin are on this combination. Occasionally, we use NPH insulin alone, and sometimes we use lente insulin alone or lente and regular insulin.

Orally Administered Hypoglycemic Agents

These patients always ask if they can take an orally administered hypoglycemic agent instead of insulin. Dr. Fajans, would you comment on this?

DR. FAJANS: When you mention orally ad-

ministered hypoglycemic agents, we think immediately of the adult diabetic, the patient in whom diabetes develops or is first diagnosed after the age of 40. If the patient is already taking insulin, he generally should require less than 40 units.

Many patients who respond best to the sulfonylureas (ORINASE® or DIABINESE®) usually could also be well controlled on diet alone if they would stay on the diabetic diet. I assume that in your question you have eliminated those patients from consideration for the time being. This leaves a group of patients who need for control either sulfonylureas or insulin in addition to diet.

DR. DANOWSKI: How do we identify such patients? How do we find out whether they can benefit from an orally administered hypoglycemic agent?

DR. FAJANS: Let us assume we are dealing with a patient more than 40 years of age who has fasting hyperglycemia and no ketone bodies in the urine. I want to emphasize that the patient must be nonketotic. We can start him on 1 gm. tolbutamide three times daily and use the fasting blood sugar as an index of response. Incidentally, I agree entirely with Dr. Danowski's viewpoint with respect to the importance of the patient's following his own disease by frequent urinalyses, but I think that determinations of fasting blood sugar are a very important complement in the physician's evaluation.

In our trials of an orally given hypoglycemic agent, we follow the fasting blood sugar levels on successive days. If over a period of a week the fasting blood sugar does not fall on 3 gm. of tolbutamide daily, the patient usually will not respond to these agents. There are a few exceptions, in which patients may respond to Diabinese simply because higher blood sulfonylurea levels can be attained. If a patient fails to respond, I would then turn to insulin. On the other hand, if the fasting blood sugar level falls, I would reduce the tolbutamide dosage, until I find the smallest dosage on which the fasting blood sugar can still be maintained at normal levels.

Occasionally, when the fasting blood sugar level returns to normal, the orally administered hypoglycemic agent can be eliminated completely. Hence, even if diet alone did not accomplish the job at one time, it may do so later.

DR. DANOWSKI: The patient who is to benefit from Orinase must have a residual ability to make insulin. The sulfonylureas enhance this residual ability, so that with the aid of dietary restriction the patient can dispose of his metabolic load in a perfectly normal fashion.

I cannot emphasize too strongly Dr. Fajans' statement about ketosis. Ketonuria is a contraindication to the trial or the use of orally administered hypoglycemic agents. This is not a point that is known to all physicians. It does not mean that if your patient has ketonuria today he can never use orally given hypoglycemic agents; however, he certainly cannot rely on them as long as this condition is present.

Brittle Diabetes

Management of brittle diabetes is another problem which should be discussed. A brittle diabetic is a patient who vacillates between ketosis and shock. First, one must be sure that the brittleness is in the patient and not in the physician. A physician who insists that he is going to make every patient normoglycemic while fasting, without undue blood sugar elevation postprandially and without glycosuria, may well produce brittle diabetes. We see a half-dozen such patients each year. They experience repeated unrecognized subclinical hypoglycemic episodes. Each episode of shock makes the diabetes more difficult to regulate because the liver becomes deglycogenated and the glucose tolerance decreases further. In an attempt to resolve the brittleness, the insulin dosage is raised successively, whereas it really should be lowered. This is one category of brittle diabetes that is readily treated.

Dr. Fajans, will you comment further on the problem of brittleness?

DR. FAJANS: I would define a brittle diabetic as a patient who, although maintaining the same diet, insulin dosage and physical activity, has marked variations in blood sugar and multiple reactions on one day and may go into ketosis the next day.

DR. DANOWSKI: Juvenile diabetics are usually placed in this category. I do want to point out, however, that occasionally you will see a juvenile diabetic who does not require insulin for a number of years.

Circulatory Problems

Dr. McKittrick, what can one do to improve the circulation in the foot that obviously has an insufficient blood supply? What nerve blocks, nerve sectionings and vasodilators may be used?

DR. MCKITTRICK: I think there probably is very little that can be done actually to improve circulation in a patient whose problem is circulatory in origin. When a patient has trouble with his feet, it is imperative to differentiate between the foot with good circulation and the one with poor circulation.

The mechanisms for helping the foot with poor circulation are indirect; they may be listed as follows: (1) hygiene; (2) avoidance of injury and accident; (3) avoidance of overuse; (4) reconstructive surgery, which is available to an increasing number of these patients; and (5) possible sympathectomy.

Some patients are greatly helped by sympathectomy; however, it is impossible to foretell by any laboratory methods which patients may be benefited. If you can see definite evidence of vasomotor activity in the foot, such as sweating or changes in color, that patient will be helped by sympathectomy.

We still use Buerger's exercises, but I do not believe they are helpful in improving the circulation. I think they only help the patient to live within his circulatory possibilities.

I know of no experimental work which has shown orally administered vasodilators to be helpful. I do think they help the doctor who gives them, and they make the patient think that something is being done for him. However, there is no evidence, as far as I know, that they are useful in improving the circulation of the patient.

Questions

QUESTION: Retinopathy is developing in a patient controlled by Diabinese. Should this patient be placed on insulin?

DR. FAJANS: Our present concept of the mode of action of Diabinese and other sulfonylureas is increased insulin release. We have no evidence at all that insulin from a bottle would do a better job than endogenous insulin released during sulfonylurea therapy. Hence, the direct answer to this question is No; however, I would like to develop this a little more. In this particular patient, not only retinopathy but also diabetic renal disease may be developing. If so, I would certainly hesitate to use Diabinese, because this agent is excreted entirely by the renal route, and if there is renal impairment, one may build up high sulfonylurea concentrations.

DR. DANOWSKI: I saw one such patient who was hypoglycemic for five days after a single dose of an orally administered hypoglycemic preparation.

This question on retinopathy touches on a very major point. The physician wishes to know what is the best way to prevent either the appearance or the progression of the small blood vessel disease which occurs in so many long-term cases of juvenile and adult diabetes. Unfortunately, it is not completely agreed that perfect diabetic regulation is the answer.

Relatively speaking, the difference between well-regulated and poorly regulated diabetics is very small in terms of the degree of vascular disease that ultimately develops. We really should put all our efforts into preventing diabetes, and hope that this will also eliminate the vascular problem. We certainly do not know how to guarantee in any one diabetic patient that after 20 or 25 years there will be no vascular disease. This is why we should direct our efforts toward prophylaxis of the diabetic state.

QUESTION: I have been using for tests and checkups on diabetic patients specimens collected two hours after breakfast, lunch, dinner and at bedtime. I believe this gives a good check. Do you agree?

DR. FAJANS: The answer is Yes if we know that the renal threshold is normal. However, with a high renal threshold the fasting blood sugar may be 300 mg. per cent in a patient who has no glycosuria.

DR. DANOWSKI: This is an excellent point.

In addition, we should not forget that the patient who does not empty his bladder completely obtains misleading test results.

Diabetic Coma

Many questions have been asked about diabetic acidosis and coma. Insulin is the *sine qua non* in the therapy of diabetic coma. When a patient in coma is being sent to us from outside the city, we ask the family physician to give the first dose of insulin before sending him in. You cannot treat diabetic coma without insulin. You give it early and in large amounts (up to 300 or 400 units in the first two to four hours). If we err, it is on the side of giving too much insulin, for we can prevent hypoglycemia by administering glucose.

In the emergency room, we withdraw a sample of blood and start an infusion of saline. Into the other arm, if we are dealing with an older or a very sick patient, we infuse dextran with saline to support the circulation.

Would you continue with this discussion, Dr. Fajans?

DR. FAJANS: After giving insulin and initiating the saline, the primary objective in a patient who is in coma is to repair the abnormalities of extracellular fluid, improve the circulation, and correct the dehydration and any hypovolemia. We use a physiologic electrolyte solution which contains less chloride than saline and more bicarbonate, because we think it helps in the severe case. After about four hours or so of therapy, if renal output is good, we direct attention to the intracellular abnormalities that one finds in diabetic acidosis and add potassium to the infusion.

As soon as the patient responds and as soon as he stops vomiting and being nauseated, we start oral feedings. We continue to use insulin at intervals, but we do not start long-acting insulin until the patient is well out of acidosis.

DR. DANOWSKI: We would like to conclude by giving you orders of magnitude for estimating deficits in adult diabetic coma, because these will identify the therapeutic goals. Remember that an adult diabetic in coma has a 10 per cent deficit of body water. Therefore, if the patient weighs 70 kg., the deficit of water is 7 liters. In addition, there is a 10 mEq. deficit of sodium and of chloride per kilogram of body weight, which is 700 mEq. of each. Such a patient also has a 5 mEq. deficit of potassium per kilogram of body weight, which is about 350 mEq. in a man weighing 70 kg.

It is important to remember that you do not have to cure the patient in the first two minutes after he enters the hospital. The physician's goal should be the prompt administration of enough insulin, support of circulation, and the correction of a portion of the life-threatening deficits. This will turn the patient toward recovery. It will provide time for the body regulatory mechanisms to make the appropriate selection of ions and of other solutes which it needs.

MEDICO SEEKS VOLUNTEERS

MEDICO, the nonprofit medical service organization providing direct aid to newly developing areas, is increasing its medical personnel serving in overseas hospitals and clinics. Requests have been received for medical and surgical teams in South America and in the newly emerging countries in Africa. In addition, surgeons, internists, general practitioners and anesthetists are needed in Afghanistan, Malaya, Laos, Cambodia, Vietnam and Haiti.

Information on salaries and length of service and specific details concerning each project may be obtained from MEDICO, Inc., 420 Lexington Avenue, New York.

Self-help Devices:

Homemaking: House Cleaning

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DESPITE pathologic and clinical differences in their disabilities, handicapped persons often have in common the need to conserve energy and to compensate for limited range of motion in bending, reaching, grasping and holding. In this article, the last of our series on aids to homemaking, are suggestions and devices to meet these common needs.

Carpet sweepers are most satisfactory for quick carpet care, and several companies are now making a miniature sweeper which is effective, lightweight and easy to manage, particularly for the homemaker in a wheel chair. Serviceable old-type vacuum cleaners can be made mobile by a dolly as shown in figure 2b. However, when planning to invest in a new cleaner, units with dusting attachments, a switch which can be easily reached, and a tank or canister on wheels should be considered. Before purchasing such a unit, the homemaker should check to see if she is able to operate it and to remove the accumulated debris.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 1. Carts provide an organized method for bringing cleaning supplies from one room to another, which saves steps and reduces stress on the arms and hands.

FIGURE 2. A dolly, either home-devised or purchased, can be used to transport pails of water (a), supplies, vacuum cleaners without wheels (b), etc. The dolly can be pushed with the foot, a cane or a crutch or pulled by an attached cord.

FIGURE 3. At times, an apron with several large pockets will suffice for carrying smaller cleaning aids. If the major problem is a disabled hand, supplies may be carried in a basket over the arm.

FIGURE 4. For ambulatory homemakers unable to bend or those confined to a wheel chair, the long-handled dustpan should be standard equipment. The accompanying short-handled broom shown here is lightweight and particularly easy to manage by the homemaker in a wheel chair who is unable to cope with unwieldy, standard-length brooms.

FIGURE 5. Dry mops with flexible handles eliminate bending to reach dust under furniture.

FIGURE 6. For wet mopping, cellulose sponges are easier to use than string mops. They are available with and without a self-squeezing mechanism. In selecting one with the squeezing device, be sure that it is set high on the mop-stick for easy reach and that the patient is able to press the button which controls the squeezer.

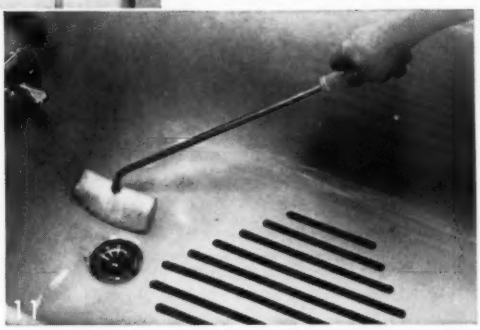
FIGURE 7. For those unable to use a squeezing mechanism because of hand impairment, it will be necessary to improvise a means of pressing out excess or soiled water. The simplest method is to span the pail with a metal plate as is shown here.

FIGURE 8. When bending is a problem, minor food spills may be wiped up with a short-handled mop or a cloth fastened to a stick. A Reacher with a cloth in its jaws (see figure 10a) is also helpful.

FIGURE 9. For dusting, a mitt-type cloth is recommended for those who have no trouble reaching and need to keep their hands in extension as much as possible to prevent or deter flexion deformities of the fingers.

FIGURE 10. When loss of reach is the main difficulty, a long-handled mopstick or a Reacher with a dustcloth in its jaws (a) can be used. A good device for narrow spaces is the Reach-All (b), a wooden shaft 27 in. long, with a jacket of vinyl sponge that can be slipped off easily for laundering.

FIGURE 11. After a tub bath, the patient with reaching and bending difficulties is urged to clean the tub while still seated in it. If this is not feasible, units such as the Tub Master provide increased reach.



The homemaking series was written in consultation with Mrs. Julia Judson, M.A., formerly homemaking consultant at the Institute of Physical Medicine and Rehabilitation. For further information on homemaking for the handicapped, Rehabilitation Monograph No. 8, "A Manual for Training the Disabled Homemaker," can be obtained by sending $2.00 to: Institute of Physical Medicine and Rehabilitation, New York University, 400 East 34th Street, New York 16. Checks and postal or money orders should be made payable to New York University.

SYMPOSIUM

Peripheral Arterial Diseases

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AND CAMPBELL MOSES[3]

Aneurysms of the abdominal aorta cannot be treated medically. Unless definite contraindications exist, operation should be performed.

Experimental studies have shown a relation between high serum cholesterol levels and atherosclerosis. The safety of the general use of triparanol in elevated serum cholesterol is still debatable.

Anticoagulants and vasodilators have not proved effective in arterial diseases.

In selected cases, sympathectomy is considered a valuable procedure.

Operation rather than use of fibrinolytic agents is recommended for most cases of emboli in the femoral or popliteal arteries.

Results of vascular surgery in diabetics have been as good as those in nondiabetics.

Aortography is not a necessary diagnostic procedure in abdominal aortic aneurysms, but is being used more frequently in hypertensive patients with possible occlusive disease.

DR. BERNARD FISHER (Moderator): Instead of presenting formal discussions, the panel will attempt to answer some pertinent questions on various aspects of peripheral arterial diseases and try to offer solutions to some of the problems of vascular surgery.

BERNARD FISHER

Aortic Aneurysms

Dr. DeBakey, do you think that operation should be performed in every case of abdominal aneurysm?

DR. MICHAEL E. DEBAKEY: There are few, if any, medical conditions in which something should always be done; however, in most life-threatening conditions for which there is some specific and curative form of treatment, the proper therapy should be carried out. In some cases therapy may have to be postponed—for example, if the anesthesia involves a risk to the patient—but, unless there is some definite contraindication, operation should be performed for an aneurysm of the abdominal aorta. As long as the aneurysm remains, it threatens the patient's life, and I do not be-

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MICHAEL E. DEBAKEY

CAMPBELL MOSES

lieve that it is possible to determine clinically just when the threat may become critical.

More than 10 patients have been admitted to our hospital with abdominal aortic aneurysms which were asymptomatic at the time of admission. While these patients were being studied for surgery, their aneurysms ruptured and a certain proportion of the patients died. We know from experience and studies in nonoperative treatment that in the natural course of this disease over a five year period only about 10 per cent of these patients will survive without operation. Thus, we believe quite strongly that unless circumstances definitely contraindicate operation, aneurysms should be removed by surgery.

DR. FISHER: Do you think the patient's age is an important factor?

DR. DEBAKEY: I am sure there is an age limit for such operations, although I must admit that we have not yet found it. I suppose that if a patient had reached an age at which he was so debilitated that only his heartbeat indicated that he was still living surgery would be contraindicated.

DR. FISHER: Certainly, the size of the aneurysm does not determine whether or not operation should be performed. It is important to emphasize that small aneurysms can rupture as easily as larger ones. A clinician should not think that because an aneurysm is small it should just be watched for a while.

Now, let us consider the diagnosis of an abdominal aneurysm. If a patient has a pulsating mass which the clinician thinks is an aneurysm, should this diagnosis be verified by aortography, Dr. DeBakey?

DR. DEBAKEY: Aortography is not necessary in the majority of cases, because, if properly taken, the plain films of the abdomen will outline the aneurysm. This is due to the little flecks of calcium in the peripheral wall. In some cases, calcium is not present or the aneurysm cannot be outlined very well; however, if the aneurysm can be felt, this in itself is a fairly good diagnostic maneuver.

We use aortography in diagnosing aneurysms under only two conditions: (1) when there is some doubt as to whether the aneurysm arises in the upper abdominal aorta and involves the renal arteries or the major visceral branches and (2) in patients with hypertension. In the first instance, aortography is done to aid us in planning operative treatment; however, this really is no longer necessary, as we can easily decide the method of approach at the time of operation. Thus, involvement of the major visceral branches does not constitute a contraindication to operation. In patients with hypertension, aortography indicates whether or not there is involvement of the renal arteries. If there is such involvement and particularly if there is occlusive disease associated with the aneurysm involving the major branches at their origin, we not only resect the aneurysm but also provide normal circulation; i.e., we treat the lesion in the renal arteries either by endarterectomy or by means of a patch graft or bypass graft at the time of operation.

Serum Cholesterol in Atherosclerosis

DR. FISHER: Arteriosclerotic disease may be seen as either aneurysmal dilatation or complete occlusion of a vessel. Dr. Moses, is there really hope that established atherosclerotic vascular disease can be reversed by medical procedures?

DR. CAMPBELL MOSES: I am glad that you distinguished between aneurysmal dilatation and atherosclerotic occlusion. As Dr. DeBakey has stated, no medical measure can insure against catastrophe in aneurysmal dilatation, whether the aneurysm is atherosclerotic or, more rarely, syphilitic in origin. The same is true at present of atherosclerotic vascular disease in man, in which the arteries gradually

corrode, with a decrease in the lumen and therefore in blood-carrying capacity. However, I do think that our experimental studies of reversing atherosclerosis medically merit some attention.

To produce atherosclerosis of the aorta and coronary arteries in the dogs on which we have been working, the cholesterol in the diet must be doubled or trebled for a year, or a tenth of the dog's life span. We can produce aortic and coronary atherosclerosis in about a year in litter mates by destroying the thyroid and giving them a high-fat diet. We have shown this to be a reversible process by sacrificing one dog as a control and restoring the cholesterol in the other litter mates to a level of about 120 mg. per cent. Under these conditions, the atherosclerosis either is reduced sharply or disappears entirely. However, this again requires a tenth or perhaps more of a dog's life span.

Because of these experiments, there is reason to think that atherosclerosis may become a reversible process in man, if we can exploit it against the parameter of time—perhaps 10 or 12 years.

DR. DEBAKEY: Dr. Moses, would you comment on the prevention of this disease?

DR. MOSES: This is the crux of the matter. We now identify those who are susceptible to the disease only after they have had a coronary or a cerebral accident. We must identify susceptible persons early. For example, two years ago, examination of the sophomore class at the University of Pittsburgh School of Medicine showed that 10 of 96 students had cholesterol levels of over 300 mg. per cent. They were totally without symptoms. Now, all these students have cholesterol values uniformly at youthful lipid levels of approximately 200 mg. per cent.

Certainly, we cannot control all phases of atherosclerosis; we cannot effectively attack the coagulation phases and we do not know how to alter the collagen changes, but we can maintain youthful lipid levels in adults. We are foolish to say we can do nothing about it. A rise in total serum cholesterol from 180 to 250 mg. per cent occurring in most adults between the ages of 20 and 55 is neither necessary nor desirable. A cholesterol level of 250 mg. per cent in a 50 year old man is definite evidence of hypercholesteremia, and, with the tools we now have to control this condition, we need not accept it as an inevitable event.

DR. FISHER: How do you explain the vascular catastrophes and vascular diseases that occur in persons who have a normal serum cholesterol level of 150 mg. per cent?

DR. MOSES: It is very important to remember that atherosclerosis is not a cholesterol problem alone. Many pathologists, more in Europe than in this country, and much data emphasize the role in atherosclerosis of coagulation changes and changes in the intramural circulation of the vessel wall. The interplay of several factors results in occlusion of the arteries. There is one factor which we can treat. The advisability of restoring a normal blood pressure in a hypertensive patient is seldom debated. I think we should no longer debate the wisdom of restoring the total serum cholesterol to the level that characterizes young adults. We can do this without gross manipulations, and I think it is a reasonable, rational thing to do.

Anticoagulant Therapy

DR. FISHER: Dr. DeBakey, do you think anticoagulants have any place in preventing the progression of atheromatous disease in patients who have minimal symptoms and who are not, in your opinion, candidates for operative procedures?

DR. DEBAKEY: We do not use anticoagulants in such patients simply because we ordinarily do not follow these patients from day to day. In our experience, we have not gained any confidence in anticoagulants or in the use of long-term anticoagulant therapy. Perhaps this is because we see patients who have been on long-term anticoagulant therapy and who nevertheless have had progressive occlusive disease or vascular accidents. For example, we see acute strokes, with precipitation of thrombosis in about 15 per cent of the patients we operate on, in spite of the fact that the patients have been on so-called effective anticoagulant therapy (i.e., having a prothrombin time of around 15 to 20 per cent of normal)

because of previous coronary artery disease.

You may find it interesting and informative to know that at the 1960 International Conference on Brain Diseases three reports were given on the use of anticoagulant therapy in cerebrovascular insufficiency. One report was a result of collaborative studies conducted by about 20 units across the country; the second report was from the Veterans Administration, and the third was from a London physician, who reported his own experiences in a London hospital. In all three studies, results in a control group, in which no therapy was used, were compared with those in a group given anticoagulants. The same conclusions were drawn from all three studies; namely, that it was not possible to demonstrate statistically any significant difference in the mortality between the control group and the treated group. It is interesting to observe that some 15 years after the introduction of anticoagulants there still is much controversy surrounding their use.

DR. MOSES: I am glad to hear Dr. DeBakey express this viewpoint. I have been interested in anticoagulants for a long time, but I am very skeptical about their value in any controlled, practical way. It is considered almost immoral, if not illegal, not to use anticoagulants in managing patients with coronary disease. There is a little more skepticism about their use in peripheral vascular and cerebrovascular problems. I believe that the incontrovertible value of anticoagulants has not been established; this is particularly evident in any symposium on peripheral vascular disease. Although this is not the place to discuss this, I am not sure that the arteries in the heart and in the brain differ significantly in biologic aspects from those of the lower legs and arms.

DR. FISHER: We have been able to demonstrate further progression of minor segmental disease in the superficial femoral or popliteal arteries in patients who have been on COUMADIN® therapy for a year or 18 months.

I think that the members of this panel obviously have little confidence in the effectiveness of anticoagulant therapy in peripheral vascular disease.

Triparanol Therapy

We hear a lot today about triparanol (MER/29®). Have you been doing any work with this agent, Dr. Moses?

DR. MOSES: Those of us who are interested in the metabolic mechanisms relating to cholesterol metabolism have found triparanol to be a most interesting compound. This drug specifically blocks the last step in cholesterol synthesis in the body. Just before the body completes the synthesis of cholesterol, desmosterol is elaborated. This compound is identical with cholesterol except for the presence of one double bond in the side chain. Triparanol specifically blocks this conversion to cholesterol.

This drug has aroused a great deal of clinical interest, since it does effect the apparent lowering of the serum cholesterol value. Actually, the lowering of the cholesterol level with triparanol is more apparent than real. The sterol which builds up in the presence of triparanol (desmosterol) gives only about 60 per cent of the color reaction seen with cholesterol in the Liebermann-Burchardt test; thus, there seems to be more decrease in sterol content than there actually is.

Ample data are now available which indicate that the compound that builds up in the blood with triparanol is desmosterol rather than cholesterol. It is possible that we now are going to be confronted with the problem of desmosterol sclerosis instead of cholesterol sclerosis. Only a very few of us are now feeding triparanol to cows in an attempt to get an adequate supply of desmosterol.

Although triparanol has been hailed because of its lack of toxicity, it does have some significant toxicity relating primarily to the liver. If those of you who are using triparanol will do some serum glutamic pyruvic transaminase levels, you will find that they consistently rise in almost every patient given this drug over a three month period. There have been three reports of the development of positive results in cephalin-cholesterol flocculation tests. In four of 10 patients to whom we gave this drug, there was a significant degree of BROMSULPHALEIN® retention.

In view of the fact that as we presently understand triparanol it is going to have to be given for years and decades, it seems a bit premature to be absolutely certain about its safety for widespread, uncontrolled use.

Treatment of Acute Occlusions

DR. FISHER: I think we should discuss another matter which always seems a bit controversial, especially among internists. This problem has to do with the treatment of acute occlusions, such as emboli in the femoral artery or the iliac artery, in patients who have myocardial infarcts. Occasionally, there is a difference of opinion as to whether or not operation should be performed in these patients. Dr. DeBakey, what is your opinion?

DR. DEBAKEY: Since it is possible to remove an occlusion of this kind (an embolus) and to restore the patency of the vascular bed with relative safety, I generally favor this form of treatment. This by no means implies that all such patients should be treated in this fashion. In some cases, the patient's condition, particularly the cardiac status, may necessitate temporizing or even postponing the operation. Usually, however, this type of condition is associated with congestive heart failure. If a patient has severe auricular fibrillation, one should attempt to improve the cardiac status; this can be done in a matter of 6 to 10 hours with intensive treatment. Thus, in many cases, it means postponing the operation for only a short period.

Some small emboli which involve the smaller vessels, for example, those in the upper extremity that may get down into the radial or ulnar branches, may not require operation. Even if they do produce a complete block, most of these will have adequate collateral circulation through other branches and thus will not jeopardize the extremity and therefore the life of the patient. However, when emboli involve the femoral or popliteal arteries, we tend to advise operation in the majority of cases.

DR. FISHER: Would you use fibrinolytic agents, Dr. Moses?

DR. MOSES: I am not satisfied with the practical value of fibrinolytic agents today. I am sure we all are interested in exploring and experimenting with them. However, if I should have a clot in my popliteal artery, I would prefer having someone take it out rather than attempt to pass some catheters down and see if it could be washed out with fibrinolysin.

Indications and Contraindications for Vascular Surgery

DR. FISHER: Let us now try to crystallize our thinking a bit on the occlusive diseases of the extremities. If a patient has a claudication with no other symptoms, Dr. Moses, how do you handle him? When do you call for a surgical consultation?

DR. MOSES: This is not an easy question to answer, and there is no simple or dogmatic rule of thumb which may be applied. The procedure would depend on the kind of person the patient is, a little on his personal and family history, and on the type of work that he does. If the patient is a bartender, the decision might be somewhat different from that in the case of a postman. A total serum cholesterol of 400 or 500 mg. per cent and a history of excessive smoking also would influence my decision as to when to ask for surgical consultation. If the patient has good femoral pulses and adequate pulses in his feet, I would temporize, instructing him in the hygienic care of his feet and prescribing a reduction in the amount of smoking, for a period of two or three months. During this period, I could obtain a clear approximation of the severity of the patient's symptoms and make an accurate appraisal of the month-to-month variation in disability.

I think we should distinguish between asking for a surgical opinion and ordering an operation for a patient. I like to get a surgical opinion very early in such cases, but I do not advise an operation before some of the other factors have been controlled.

DR. FISHER: Would you comment on this, Dr. DeBakey?

DR. DEBAKEY: I would generally agree with Dr. Moses. One certainly should know something about the patient's general condition; for example, I think it is important to know his cardiac status. Our experience generally

indicates that if a patient has an atherosclerotic occlusive lesion in one part of the body it is possible, in fact, probable, that the condition also may exist in some other vital segment of the arterial bed. Certainly, it is important to know whether or not the coronary artery is involved.

About 30 per cent of the patients on whom we have operated have coronary artery disease in association with atherosclerotic lesions of the peripheral arteries. So you see the importance of knowing this. If a patient has capacity-limiting coronary artery insufficiency, I do not think it is desirable to operate on him for a well-localized segmental lesion involving the superficial femoral artery and producing some intermittent claudication if that lesion does not threaten the extremity because of good collateral circulation. We sometimes see patients with angina as well as intermittent claudication. Thus, I think that as long as the occlusion of the artery of the extremity does not threaten the limb or cause severe disability, it might not be wise to operate merely to restore normal flow. The patient should be treated just as Dr. Moses recommended.

DR. FISHER: We all agree then that when claudication is the only symptom and the cardiovascular system is in reasonably good condition only those patients who must be on their feet in the course of their work should be considered potential candidates for surgery. Certainly, the man who always has been able to play 18 holes of golf and who finds that he can no longer do so is not seriously considered a candidate for surgical intervention for this reason alone.

If a patient has rest pain or has trophic changes, the situation becomes a little different, and we would be more inclined to perform an operation. As Drs. DeBakey and Moses have said, these persons should be operated on unless surgery is contraindicated by severe cardiovascular or renal disease.

Dr. DeBakey, are there any other contraindications to peripheral vascular surgery?

DR. DEBAKEY: One must assume, of course, that the arterial lesion is operable.

DR. FISHER: How do you determine whether or not a lesion is operable?

DR. DEBAKEY: In the majority of cases, this can be determined very effectively by means of arteriography. If the lesion is localized so that at least a good portion of the distal arterial bed is patent, it is operable. This is true even if the lesion extends as far down as the branching of the popliteal artery.

We had one case which represented a slightly more extensive approach. In this patient, only the anterior tibial artery was patent. All other branches of the popliteal artery, as well as the entire popliteal artery, were blocked. On the basis of arteriography, we probably would have considered this an inoperable case; however, the extremity was being threatened. The patient had gangrene of the toes and such severe rest pain that an operation was obviously necessary; we also thought that we would have to perform an amputation above the knee. We did operate on this patient (as an exploratory procedure in a sense) and did a bypass graft to the tibial artery as a sort of last resort to try to save the extremity. The operation proved successful, and the extremity was saved.

We know from our own experience that a certain proportion of these procedures will not be successful, because the flow through that one remaining vessel is simply inadequate. Of course, nothing is lost by trying the graft; the operation must be done anyway. It is possible to tell whether or not it will be successful at the time of operation. When a graft is not successful, it adds only about a half-hour to the total operation time, since the amputation must be done anyway.

Arteriography

DR. FISHER: Do you believe there is any danger or risk worth considering in performing arteriography?

DR. DEBAKEY: In our experience, arteriography is associated with less than a 1 per cent total risk. This conclusion is based on several thousand arteriograms. I think that the risk may be considered as perfectly justifiable in terms of the advantages of arteriography and the nature of the disease. I would not say that arteriography does not involve any risk; there is a risk in even a simple venous puncture.

In fact, there is a risk in almost any procedure, but the degree of risk varies; it must be evaluated in relation to the advantages of the procedure, the information to be derived from it, and the nature of the disease. Considering these factors, I think the risk of arteriography in proper hands is so small that it should be performed.

DR. FISHER: When should we do carotid arteriograms, Dr. DeBakey? If a patient has a stroke, should he have a carotid arteriogram? Which patients are the most likely candidates for this procedure?

DR. DEBAKEY: I think that an arteriogram should be done in every patient who has an acute stroke without manifestations of an intracranial hemorrhage, a tumor or a ruptured berry aneurysm, or in whom a lumbar puncture fails to show blood.

DR. FISHER: Do you agree with this opinion, Dr. Moses?

DR. MOSES: Yes, I do agree. I think it is time that we realize it is possible to do something about strokes other than just observe the patient.

Sympathectomy and Vasodilators

DR. FISHER: If a patient is not amenable to vascular surgery, do you recommend sympathectomy? This procedure has been used for many years. When do you advocate its use, Dr. DeBakey?

DR. DEBAKEY: I am an advocate of sympathectomy, because I have learned that in some circumstances it is a very beneficial procedure. I have followed patients for over 20 years who have had a sympathectomy and who have maintained viability of their extremities. Although I have not observed a great deal of improvement in intermittent claudication with this procedure, it has been noted in some patients, probably due to development of collaterals over that period of time. However, in comparison with patients who have not had sympathectomy, patients in whom it has been performed have shown definite improvement; thus, we think highly of this procedure. We use it in patients who have peripheral diffuse arterial disease involving the distal arterial bed and in whom there is no possibility of restoring normal circulation through the main arterial channel. In some patients who have the combined forms of the disease—diffuse arterial disease and high segmental occlusive disease—and in whom it is possible to restore normal flow through the main arterial channel at the high level, we combine this procedure with sympathectomy.

DR. FISHER: Dr. Moses, what do you think about the use of vasodilators in these patients?

DR. MOSES: I do not know of a vasodilator which would alter the course of this disease, although there may be one. A new one is introduced every year or two. I think it is perfectly all right to try these agents, but I have not yet found a peripheral vasodilator which I thought was effective in either segmental occlusive disease or the more distal vascular lesions.

From the medical standpoint, I would like to endorse Dr. DeBakey's evaluation of sympathectomy. My only problem in this procedure is to determine or to predict in which patients the procedure will be successful or will effect improvement. I have not been able to predict success with any degree of accuracy. Would you comment on this, Dr. DeBakey?

DR. DEBAKEY: We have tried many different methods of determining the cases in which sympathectomy will be successful. None of these methods have proved sufficiently reliable to be used routinely; in fact, we use chiefly our clinical judgment in selecting cases for sympathectomy.

I will say that there is very little chance of success with sympathectomy in patients who have rather severe atrophy of the soft parts of the extremity (the so-called skeletonized type of extremity). Neither will it be of much benefit to patients who have very severe rest pain, ischemic change that progresses up the foot, and a skeletonized extremity. On the other hand, we have performed sympathectomy in some cases as a last resort, and we have obtained very good results with it. However, other than employing clinical judgment which comes from experience, there is really no way to predict with a high degree of accuracy the value of sympathectomy.

I want to add just one more point to what

Dr. Moses said about the use of vasodilators. Some years ago, Dr. Burch and I made a very thorough study of a number of vasodilators then available in an effort to determine their value. We studied them by using plethysmography, and we found that none of them proved effective. Frankly, I do not think that they ever will be effective, because vasodilatation can be produced only intermittently. Even the chronic vasodilatation produced by sympathectomy is tempered over a period by the return of tone in the vessels distally. The patient improves only when there is improvement in general collateral circulation over some time, which really is a result of the natural production of collateral circulation.

I might just add that alcohol is about as good as any of the various vasodilators, and for many people it is probably the most pleasant to take.

DR. MOSES: Unfortunately, the effect of alcohol is not uniquely vasodilatation.

Vascular Disease in the Diabetic

DR. FISHER: A point always brought up in any discussion of peripheral vascular disease is whether or not the diabetic differs from the nondiabetic insofar as vascular disease and amenability to surgery are concerned. What do you think, Dr. Moses?

DR. MOSES: We do not know whether atherosclerosis of the diabetic differs from that in the nondiabetic; however, there is some evidence that the metabolic pattern of the artery in the diabetic is different from that in the nondiabetic.

Since the discovery of insulin, our attention in the problem of diabetes has been directed toward the carbohydrate phases of this disease, in that insulin has prevented the deaths from errors in the carbohydrate metabolism and from acidosis. Until very recently, we have not directed much attention to the lipid phases of diabetes, and the progression of atherosclerosis in the diabetic has been in part due to this fact. I think it is time for us to study the lipid phases of this disorder, since it is now vascular disease rather than diabetic coma or electrolyte depletion which is proving fatal to diabetics.

I believe that in a hospital which has a competent laboratory and where reasonable attention can be paid to the patient, the severity of the diabetic state before it is controlled should not influence a decision as to whether or not operation should be performed. Of course, operation should not be performed in the presence of acidosis or gross electrolyte depletion, but, after these conditions have been corrected, I think that operations can be done in most diabetics, except in the presence of severe coronary disease or other cardiovascular complications.

DR. FISHER: Have you found that operative results are as good in the diabetic as in the nondiabetic?

DR. DEBAKEY: In our experience, the results in diabetic patients who have operable conditions are as good as those in nondiabetics. There is no difference in mortality and morbidity between these two groups, since the diabetes can be controlled quite effectively.

I agree with Dr. Moses in that some difference in the diabetic does add another factor to the picture of atherosclerosis. For example, younger diabetics exhibit the same degree of atherosclerosis as that seen in older nondiabetics, and the diabetic often tends to have a more diffuse form of the disease. Smaller arteries and the distal arterial bed are more frequently involved in diabetics than in nondiabetics. However, well-localized segmental disease in the major arteries can be managed just as effectively in the diabetic as in the nondiabetic.

DR. MOSES: Metabolic vascular disease in diabetics is specifically abnormal, particularly in the eye and in renal circulation, in which specific problems recently have been identified.

Recurrent Occlusions Following Surgery

DR. FISHER: A plethora of questions has come from the floor, and one which has been asked most frequently is in regard to the percentage of initially successful grafts which later become occluded. What is this percentage, Dr. DeBakey?

DR. DEBAKEY: The percentage of occlusions recurring after initially successful grafts varies

according to the site of the graft. Our experience has been the most extensive and we have done the longest follow-ups with grafts of the aorta. In this region, the incidence of recurrences over a five year period is very small, something in the neighborhood of 4 per cent. Actually, it is less than that for the abdominal aorta. These are cases that include the major iliac arteries at the bifurcation; they are not recurrent cases in the iliac arteries. With very few exceptions, these have been reoperable; i.e., it has been possible to restore normal circulation distal to the occlusive lesion which is, again, high and localized.

In the smaller vessels, such as the femoral arteries, the incidence of recurrent thrombosis is much higher. In our experience, the recurrence has been around 25 per cent over a two to five year period.

Aortography in Hypertension

DR. FISHER: We also have been asked about aortograms in hypertensive patients. Dr. DeBakey, when should a hypertensive person have an aortogram if an operation is being considered?

DR. DEBAKEY: It is difficult to answer this question categorically, because as we gain more experience with this problem, we tend to do aortography more often in order to find out which patients have hypertension due to an occlusive lesion of the renal arteries. This is a much more common form of hypertension than we have realized in the past. Like anything else, the more you look for it, the more frequently you find it. I am not yet prepared to say that one should resort to aortography in all forms of hypertension. We know that there are some specific forms of hypertension; in fact, probably most hypertension is caused by other factors.

We do not know what causes some forms of so-called essential hypertension. It may well be that some of these are related to occlusive or more distal occlusive lesions in the renal arteries, even in the smaller branches within the kidneys. For example, we know that a small accessory renal artery that is partially occluded to only a segment (perhaps about a fifth of the total kidney area) can produce severe hypertension and can be relieved by the removal of that area. We know that hypertension can be produced by partial occlusive vascular disease of the kidney.

We handle this problem by first having our internists and cardiologists try to reach some conclusion regarding the nature of the hypertension, particularly if it is a form that is difficult to control by medical measures. When it becomes obvious that rather intensive measures should be used which create additional problems for the patient and no other cause can be found for the hypertension, the possibility of an occlusion should be investigated and aortography may be the only means by which this can be done. We have tried various other so-called screening tests, but none have proved entirely reliable; thus, we have finally resorted to using aortography in the majority of cases, and in many instances we use aortography as the first specific test.

DR. FISHER: During the past year or two, we have had some misleading results with various screening tests such as scanning over kidneys, use of split sodium, and differential catheterization. Therefore, I would agree with Dr. DeBakey that direct aortography is the best diagnostic method.

Concluding Comments

DR. FISHER: Would either of you care to mention anything else of importance which we have not discussed?

DR. DEBAKEY: I think we should point out that according to recent studies the original concept of Buerger's disease may not be correct. Many patients, even in the 20 and 30 year old age group, may have an occlusive form of atherosclerosis which involves the major arterial vessels but not the distal arterial bed and which can be relieved completely. Of course, these patients are the most gratifying of any to treat, because they are so young. Normal circulation can be restored even if they have gangrene of the toes.

DR. MOSES: The only comment I would like to add is that we should attempt to identify people who have abnormalities in the lipid component of atherosclerosis before they drop dead on the golf course at age 45 or 50.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Donnelly, M.D., Chief, Section of Hematology

Leukemia, Fever and Coma

Case Report

A 72 YEAR old man first entered Hines Veterans Administration Hospital in June 1953 for evaluation of papulovesicular and erythematous cutaneous eruptions which had appeared sporadically, singly and in crops since 1940, when he had chickenpox. Painless swellings in the neck, axillae and groins had been treated with roentgen rays in 1951, 1952 and March 1953. The patient appeared well. He weighed 135 lb. The tip of the spleen was palpable. The liver was not enlarged. Minimal bilateral cervical, axillary and inguinal lymphadenopathy was present. Ovoid erythematous lesions involved all extremities. The hemoglobin value was 14 gm. per 100 ml. The leukocyte count was 23,200 per cubic millimeter; 90 per cent were mature lymphocytes. The bone marrow was normocellular with adequate megakaryocytes; the ratio of normoblasts to leukocytes was 1:4, and lymphocytes were not increased. The cutaneous lesions cleared spontaneously.

In May 1955, the patient was readmitted, complaining of a mild tendency to bruise easily and of occasional night sweats. He weighed 140 lb. The spleen was palpable 4 cm. and the liver 3 cm. below the costal border. There was generalized lymphadenopathy, the nodes being not more than 1.5 cm. in diameter. The hemoglobin value was 11.5 gm., the leukocyte count 470,000, and the platelet count 90,000. Serum albumin concentration was 4.7 gm., and globulin 2.4 gm. per 100 ml. The value for urinary urobilinogen was not increased. Results of the antiglobulin test were negative. A roentgenogram of the chest was normal. Spray roentgen-ray therapy was given to the trunk.

From June through October 1955, the leukocyte count increased from 23,000 to 100,000. The hemoglobin value stabilized at 13 gm. There was no bruising.

On February 20, 1957, the patient again entered the hospital. The capriciously appearing and resolving herpetiform lesions had continued, especially on the buttocks and thighs. The leukocyte count was 500,000. The patient weighed 143 lb. The spleen extended 8 cm. and the liver 2 cm. below the costal border. Lymph nodes were unchanged. The prostate

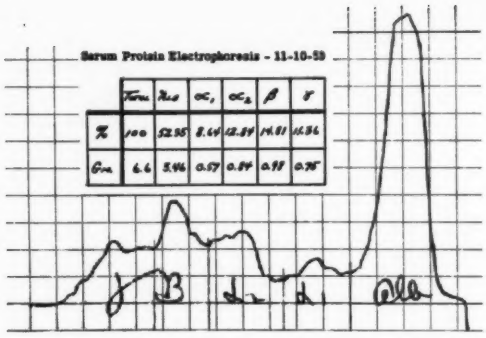

FIGURE 1. Results of paper electrophoresis of serum proteins.

was greatly enlarged. A vesicle on the right buttock, 1.5 cm. in diameter, was encircled by a 4 cm. area of erythema. The hemoglobin value was 9.5 gm., and total serum bilirubin 0.7 mg. The antiglobulin test gave positive results. Body-spray roentgen-ray therapy was given, followed by local bilateral roentgen irradiation of the regions of the lumbar nerve roots. When the patient was dismissed on May 22, the spleen extended 5 cm. and the liver 4 cm. below the costal margin, the leukocyte count was 6900, and the hemoglobin value was 10 gm.

On June 18, 1958, the patient was readmitted because of a nonhealing ulcer on the penis. The ulcer was tender, with serpiginous and slightly elevated margins and a necrotic base. There was severe penile edema. Lymph nodes were less than 1.5 cm. in diameter. Other findings were unchanged. The ulcer changed little following two months of intensive local treatment, but after local roentgen-ray therapy it healed completely.

The fifth hospitalization, on January 20, 1959, was prompted by passage of dark urine for two weeks. The spleen was palpated 7 cm. and the liver 5 cm. below the costal margin. The hemoglobin value was 12.9 gm. The leukocyte count was 161,000 with 90 per cent lymphocytes. Total serum bilirubin concentration was 4.0 mg.; the direct fraction measured 1.7 mg. Aspiration of sternal bone marrow showed moderate hypercellularity and normal megakaryocytes; ratio of normoblasts to leukocytes was 1:1. Lymphocytes comprised 15 per cent of the nucleated cells. The patient was treated with prednisone, 20 to 40 mg. daily, until May 7, 1959. During this period the hemoglobin value ranged from a low of 6.3 gm. to a high of 11.5 gm. on April 1. Reticulocyte counts ranged from 7.8 to 37 per cent. The serum bilirubin value gradually fell to 1.2 mg. Pneumonia involved the lower lobe of the left lung in late March but responded promptly to procaine penicillin. In May, a course of roentgen-ray therapy was given to a necrotic ulcer of the right buttock. When the patient was dismissed on August 13, the hemoglobin value was 12.0 gm. and the leukocyte count was 122,000.

On October 26, 1959, the patient was hospitalized for incision and drainage of an abscess in the left side of the neck. Cultures of the abscess yielded hemolytic streptococci but were negative for tubercle bacilli or fungi. Results of paper electrophoresis of serum proteins on November 10 are shown in figure 1.

The final period of hospitalization began on March 14, 1960, following recurrent bouts of gross hematuria. The patient weighed 142 lb. Blood pressure was 120/80 mm. Hg. As on previous examinations, the heart was normal. The lungs were clear. The spleen was palpable 6 cm. and the liver 2 cm. below the costal border. The prostate was enlarged. Urinalysis revealed a specific gravity of 1.020, 1 plus protein, no casts, and moderate microscopic hematuria and pyuria. Hemolytic *Staphylococcus albus* was cultured from the urine. The hemoglobin value was 9.1 gm. The leukocyte count was 190,000, with 98 per cent lymphocytes. The blood urea nitrogen concentration was 13.3 mg., and the value for creatinine 1.3 mg. per 100 ml. Serum albumin measured 5.0, and globulin 1.4 gm. An excretory urogram showed a distorted bladder shadow, suggesting prostatic enlargement. Cystoscopic examination on April 4 confirmed the presence of prostatic enlargement with obstruction of the bladder neck. Because of continuing hematuria, blood transfusions were given.

Suprapubic cystostomy was performed on April 20. Stones or tumors were not found.

The prostate was enlarged and intravesical. During the next 23 days, hematuria continued and transfusions of whole blood averaging 430 cc. daily were required. Twenty-two days postoperatively the platelet count was 79,000, the bleeding time was 13 minutes, and the reticulocyte count was 1.9 per cent. Direct-reacting bilirubin measured 0.6 mg., and indirect-reacting 1.4 mg. Urine cultures revealed *Klebsiella* species, *Proteus* species, and *Streptococcus faecalis*. Blood cultures were sterile. A roentgenogram of the chest showed clear lung fields and a normal cardiac silhouette.

Following cystostomy the patient had a hectic fever with daily spikes to 102° F. On the twenty-second day postoperatively, administration of steroids and chloramphenicol was begun. Subsequently, transfusions were not needed. The temperature stabilized, usually being less than 100° F. By the thirtieth day the patient was able to be out of bed for short periods. The leukocyte count was 283,000, with 92 per cent lymphocytes and 8 per cent neutrophils. The platelet count was 200,000, and the hemoglobin value was 12.5 gm.

On the thirty-fifth day after cystostomy, the patient was slightly confused. Over the next four days he became profoundly lethargic, responding only to noxious stimuli. Urinary output remained normal. The blood urea nitrogen concentration was 35.4 mg. and the creatinine measured 1.7 per cent. On the fortieth day the patient had a generalized convulsion, which was followed by coma and flaccid quadriplegia. Respirations became labored and there were signs of pulmonary congestion. The temperature rose to 102° F. The patient died on the forty-first day after operation.

Discussion

DR. STEVEN O. SCHWARTZ (consultant, medical service): To review the case, we have a man with chronic lymphocytic leukemia who responded remarkably well to irradiation therapy but already exhibited evidence of thrombopenia, which usually is a therapeutically troublesome and prognostically unpleasant complication of this disease. Two of several possible mechanisms for the development of thrombopenia are replacement of megakaryocytes by lymphocytic infiltration of the bone marrow and destruction or sequestration of platelets by the enlarged spleen.

After June 1955, the patient was well for about a year and a half. Herpetiform lesions appeared intermittently, especially on the buttocks and thighs. By February 1957, the leukocyte count had risen to 500,000, yet he had gained 3 lb. The spleen was now palpated 8 cm. below the costal margin, having enlarged considerably in four years. Lymph nodes were unchanged. A new finding, enlargement of the prostate, raises the possibility of benign prostatic hypertrophy. Carcinoma or lymphomatous infiltration also has to be considered, but since the prostate was not described as particularly hard, carcinoma is the least likely of the three. There was also a 1.5 cm. vesicle on the right buttock, encircled by a rather large area of erythema.

Most disconcerting is the fact that the hemoglobin value was down to 9.5 gm. Although the total bilirubin concentration was normal, the antiglobulin test gave positive results. It is obvious that abnormal globulins had developed which were coating the red blood cells. That this coating of the red blood cells was already responsible for an occult hemolytic anemia (not yet reflected in an elevation of bilirubin) is only conjectural at this point, but other evidence suggests that it was at least partly responsible. The patient was again treated by irradiation of the trunk and lumbar nerve roots, probably because it was assumed that the vesicular lesions were due to nerve involvement by the lymphoma. Three months later he was dismissed, having shown improvement not only in shrinkage of the liver and spleen but also in the leukocyte count and hemoglobin value.

About a year later, when he was 70 years old, he had an ulcer on the penis which was tender, had a necrotic base, failed to respond to local treatment, presumably did not contain spirochetes, and eventually cleared only after irradiation. This ulcer either represented a specific infiltration or was related to the herpetiform lesions.

In January 1959 the hemoglobin value was 12.9 gm. in spite of a total bilirubin concen-

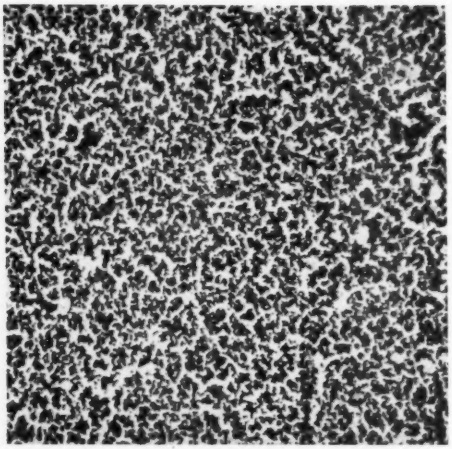

FIGURE 2. Low-power photomicrograph of lymph node showing complete effacement of architecture and infiltration by small mononuclear cells.

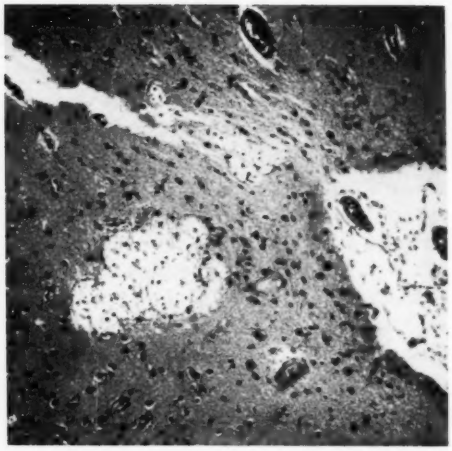

FIGURE 4. Low-power photomicrograph showing two areas of cystic degeneration of brain substance.

tration of 4 mg., with an indirect fraction of 2.3, and a two week history of passage of dark urine. The ratio of nucleated red blood cells to white blood cells in the marrow was 1:1. We now have several pieces of evidence favoring the diagnosis of a hemolytic process, which we could have anticipated from the positive antiglobulin test. The hemolytic process at this point was compensated, as evidenced by a hemoglobin value of 12.9 gm.; however, its presence is verified by the 1:1 normoblast-leukocyte ratio in the marrow, the indirect-reacting bilirubin value of 2.3 mg., the deterioration of the hemoglobin value over the next month to 6.3 gm. and the rise in reticulocytes to 37 per cent. The institution of prednisone treatment indicates that the attending physicians were thinking along similar lines. He recovered from the hemolytic anemia, but not without the development of pneumonia. Steroid therapy was continued, supplemented with penicillin. A second complicating infection (prostatism) and a third (a necrotic ulcer of the right buttock) occurred. Somehow by the middle of August, seven months after admission, he recovered sufficiently from the hemolytic episode, pneumonia, prostatism and necrotic ulcer to be dismissed.

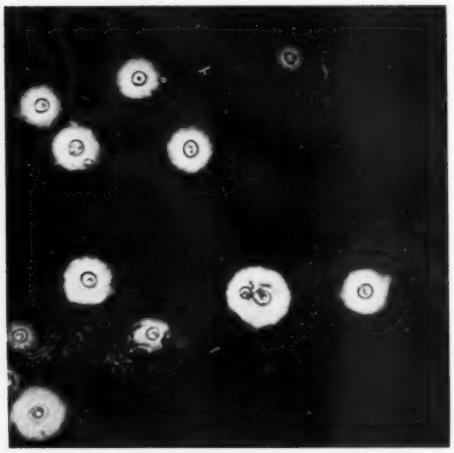

FIGURE 3. High-power photomicrograph of India-ink preparation of cerebrospinal fluid showing *Cryptococcus neoformans* with characteristic thick capsule.

Two months later an abscess in the left side of the neck was incised and drained. It contained hemolytic streptococci, but neither tubercle bacilli nor fungi were found. The antiglobulin test again gave positive results, but the total bilirubin was not greatly elevated.

The final hospitalization, beginning in March 1960, followed recurrent episodes of gross hematuria. The patient still had not lost weight, his heart was normal, and the lungs were clear. The liver, spleen and prostate still

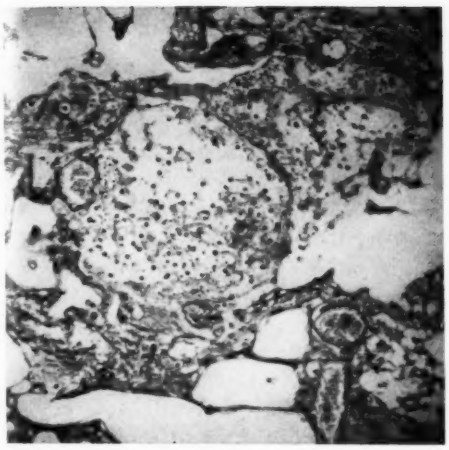

FIGURE 5. Low-power photomicrograph of lung showing granuloma filled with PAS-positive cryptococci. Periodic acid-Schiff stain.

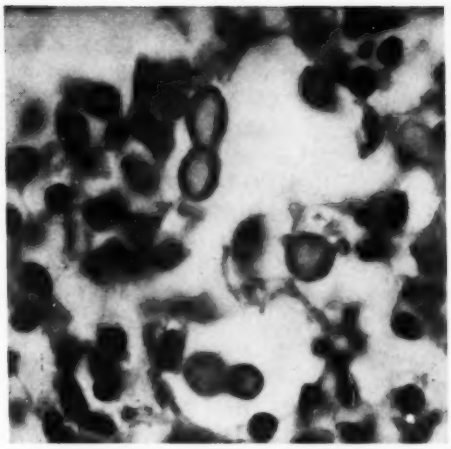

FIGURE 6. High-power photomicrograph of spleen showing scattered mycotic organisms.

were enlarged. The urine contained 1 plus protein, there were some hematuria and pyuria, and culture demonstrated hemolytic *Staph albus*. The hemoglobin value was down to about 9 gm. and the leukocyte count was 190,000. Blood urea nitrogen measured 13.3 mg., the creatinine value was 1.3, and for the first time changes in the serum albumin concentration were reported. This is not entirely correct, because the electrophoretic pattern on November 10, 1959, already showed a somewhat lowered albumin peak, slight elevation of alpha$_1$, alpha$_2$ and beta globulins, and some lowering of gamma globulin. Roentgenologic examination of the bladder revealed prostatic enlargement.

Hematuria continued, necessitating several transfusions and, eventually, suprapubic cystostomy. Stones or tumors were not found; the prostate was enlarged and intravesical. Transfusion requirements over the ensuing 23 days amounted to about 430 cc. of whole blood per day, or approximately six transfusions a week; this is equal to about 18 cc. an hour. It is unlikely that bleeding of this magnitude was related to the operative incision. Then why was the patient bleeding so severely? Possibly he again had thrombopenia. But 22 days after operation the platelet count was 79,000 and the bleeding time was 13 minutes. If the platelets were functionally adequate, this count would not be low enough to explain the bleeding, but functional inadequacy of the platelets could be responsible. Another possibility is the presence of a fibrinolysin, and this would be more plausible if carcinoma of the prostate were present. We also have to consider a coagulation defect, possibly consequent to the underlying lymphoma; when this occurs, it manifests itself as a deficiency of plasma thromboplastin component or antecedent. It is much more likely that bleeding did not account for all the blood loss; the bleeding must have been complicated by hemolysis. Bear in mind that by this time the patient's marrow was extensively replaced by lymphocytes. Thus, there are at least three possible reasons for the massive transfusion requirements, and as we go further we can get some information from the response to treatment. Parenthetically, in spite of an indirect-reacting bilirubin value of 1.4 mg., the reticulocyte count was only 1.9 per cent; so we are dealing with an uncompensated hemolytic anemia.

Following cystostomy the patient's temperature spiked to 102° F. daily. A number of organisms were recovered from the urine, but blood cultures remained sterile and a roent-

genogram of the chest was normal. Why did he have such a high fever when blood cultures were sterile and the operative wound was draining freely? Was there some change in the underlying disease? Was a new disease developing? Were all the findings related somehow to the operation?

Apparently nothing was done about the fever until 22 days after the operation, when administration of steroids and chloramphenicol was begun. Two days later, transfusions were no longer needed and the temperature was less than 100° F. It is hard to ascribe these benefits to the chloramphenicol unless, in spite of negative blood cultures, the patient had a bacteremia. More likely the effects were the result of the steroid therapy. The decrudescence of the fever, of course, is a nonspecific response and means very little, but the diminution of transfusion requirements suggests that the steroids effected a reduction of the occult hemolysis. They also may have had some beneficial effect on the blood vessels and platelets, allowing the patient to become compensated. The improvement was so dramatic that eight days later he was out of bed. The leukocyte count remained high, but platelets numbered 200,000 and the hemoglobin value was normal.

In spite of this improvement, on the thirty-fifth day he became confused. Confusion in a patient receiving steroids may be related to the drugs, but it seems more logical that it was related to infection, since the patient previously had exhibited an unusual susceptibility to infection. It has been our experience that patients with chronic lymphocytic leukemia in whom central nervous system symptoms develop most likely have either a fungous or a tuberculous infection of the central nervous system. A brain abscess also must be considered, as must severe bacteremia in view of the history of urinary tract infection. My first choice is a meningitis; on the basis of probability, cryptococcal meningitis is the most likely. The patient became lethargic and responded only to noxious stimuli. Urinary output remained good, but the blood urea nitrogen concentration rose to 35 mg. with an accompanying rise in creatinine. A generalized convulsion occurred, followed by coma and quadriplegia. Respirations became labored, there were signs of pulmonary congestion, fever returned, and the patient died 41 days after operation.

Chronic lymphocytic leukemia is the only major diagnosis we can make on the basis of the evidence and the nine year history. We know that he had a functional as well as a quantitative hypogammaglobulinemia, the functional being more important than the quantitative because it allows the postulation of a predisposition to infection. However, a patient, especially one who has multiple myeloma, may have high levels of gamma globulin and still have a *functional* inadequacy thereof. The hypogammaglobulinemia undoubtedly was responsible for the susceptibility to infection, but the steroid therapy as well as the diminished number of granulocytes unquestionably played contributing roles. The terminal illness, which we assume was due to a central nervous system infection, probably was also related to this defect. The secondary complication was hemolytic anemia; this is quite well substantiated. It is noteworthy that in spite of extensive disease the patient responded well to treatment of severe hemolytic anemia and was able to achieve compensation with the help of steroid supplementation. On the basis of probability rather than evidence, we may assume further that he had a prostatic enlargement due to lymphomatous infiltration.

Finally, we come to the question of the cutaneous lesions, which were present for about 20 years and supposedly started as chickenpox. Herpes zoster is common in leukemia or lymphoma and may antedate the underlying disease by months or years; occasionally it occurs as a complication in the course of treatment. The association of the two diseases is too frequent to be merely coincidental. Whether or not the herpes zoster is simply a consequence of diminished resistance is difficult to say. We also know that chickenpox and herpes zoster are related etiologically, and it is not illogical to expect these patients to be more susceptible to chickenpox just as they are to herpes zoster. This patient probably harbored the virus responsi-

ble for the evanescent cutaneous lesions in much the same way that most of us harbor the herpes simplex virus. The intermittent herpetiform lesions probably were related to the waxing and waning of his illness or his immunologic milieu. To speculate even further and assume that the herpetiform lesions, which presumably were due to a virus, and the leukemia were causally related would be carrying things beyond the realm of accepted facts but not entirely into the world of fantasy.

Pathologic Findings

DR. MYRON E. RUBNITZ (chief, laboratory service): At necropsy the clinical diagnosis of chronic lymphocytic leukemia was confirmed. The bone marrow was almost entirely replaced by small, mature lymphocytes. Diffuse infiltration by mature lymphocytes had effaced the normal architecture of the lymph nodes (figure 2).

The brain and meninges appeared normal grossly, but microscopic examination of the cerebrospinal fluid revealed many small round bodies, some of which appeared to be budding. When a small amount of India ink was added to the fluid, a thick capsule could be seen surrounding each body (figure 3). These findings are characteristic of the fungus *Cryptococcus neoformans*. Microscopically the meninges were edematous. Within the substance of the brain were many areas where clusters of cryptococci had invaded and destroyed normal tissue (figure 4). Characteristically, there was little or no inflammatory reaction adjacent to these areas; meningitis due to bacterial or other fungous disease usually is attended by inflammatory or granulomatous reaction.

The lungs were a little heavier than normal but grossly exhibited only a few areas of induration. Microsections showed definite bronchopneumonia and many focal accumulations of cryptococci. Periodic acid-Schiff staining demonstrated the fungi well (figure 5).

The liver was grossly normal, but microscopically there was periportal infiltration by mature lymphocytes, a finding characteristic of chronic lymphocytic leukemia. Many small aggregates of cryptococci also were seen throughout the liver.

The spleen weighed 700 gm., about five times the normal weight. Microscopically the architecture was replaced by diffuse infiltration of mature lymphocytes. Cryptococci also were seen throughout the spleen (figure 6).

The kidneys and adrenal glands were grossly normal, but microsections showed areas of invasion by mature lymphocytes, representing leukemic infiltrates. In both organs there were areas of destroyed tissue in which cryptococci could be identified easily.

Examination of the prostate revealed only changes consistent with chronic prostatitis.

Summary of Diagnoses

Clinical diagnoses—Chronic lymphocytic leukemia; auto-immune hemolytic anemia; herpes zoster; benign prostatic hypertrophy with obstruction.

Dr. Steven O. Schwartz's diagnoses—Chronic lymphocytic leukemia; auto-immune hemolytic anemia; herpes zoster; prostatic enlargement due to leukemic infiltration; meningitis due to *C. neoformans*.

Anatomic diagnoses—Chronic lymphocytic leukemia; cryptococcosis, generalized, involving meninges, brain, lungs, liver, spleen, lymph nodes, kidneys and adrenal glands; chronic prostatitis.

Portrait of the Doctor: In Prehistoric Days and Antiquity

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"The most interesting surface in the world is the face of the human being."—Lichtenberg.

A PORTRAIT differs from a caricature in that its goal is to reproduce the natural, unaccented, real and unexaggerated image of the individual. A caricature frequently presents an individual with a comic unreality which may appear more truthful than a natural portrait.

While the intention to draw a caricature usually originates with the artist, a portrait is often commissioned by a "model" or by someone who wishes the "model" to be portrayed.

A portrait often expresses the character of the subject (painter) as the personality of the object (model). The degree of empathy or hostility between the two will find representation in unusual accents and emphasis.

Regardless of the motive for making it, a portrait transmits an individualistic understanding of the psychology of the object's facial expression, his thoughts and desires, his character values and misgivings. The portrait painter (even in a commissioned work) will find fascination in the mimic play, in the form and movements of the hands, in the beauty of the body in motion or repose. These aspects of the human personality must impress him enough to become the prime source of his interest, which he attempts to capture and treasure on the canvas. A portrait painter must have considerable understanding of anatomic structure and function, either through study of anatomy or through careful visual observation.

Real portraiture is a form of painting which had its beginnings in earliest recorded human history. Its birthplace, however, was Egypt, where portraits of Niank Prah (circa 2650 B.C.) have been found. They are still preserved in the burial place of Ptah-Hotep in Sakkara near the Pyramids.

The great art of the Greeks and Romans was governed by the idealization of human beauty and the adoration of personified gods and goddesses. Only in the paintings on Grecian vases and in the golden death masks covering the faces and bodies of named personages do we find portraits. These predominate in Cretan and Mycenaean art.

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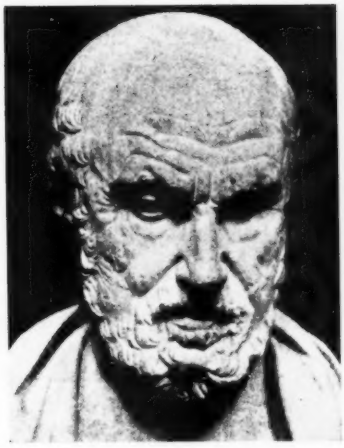

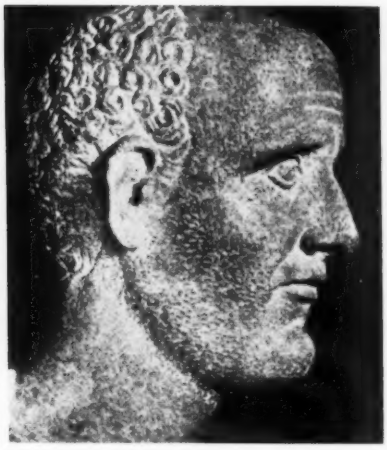

Imhotep, circa 3000 B.C. (*left*). Physician of Pharaoh Zoser, great architect (pyramid of Sakkara), priest, statesman, demigod in Egyptian mythology. Sculptures are in the British Museum, in Berlin and in Cairo. Imhotep was generally depicted in a standing or sitting position, always holding an open scroll in his hands.

Hippocrates, circa 460-377 B.C. (*center*), was born on the island of Cos. This bust was found in Alban and was considered for a long time to be his portrait. It has been proved to be the head of the Stoic philosopher Chrysippus. None of the sculptures purported to be portraits of Hippocrates have been positively identified as such.

Asclepiades, circa 125 B.C. (*right*), great Roman physician from Prusa who introduced Grecian medicine in Rome. A great philosopher and very successful as a therapist, he was known to be a friend of Cicero and of Mark Antony.

Yaphyx shown treating the wounded leg of Aeneas in the battle before Troy. This scene appears in a Pompeian wall painting dating from the first century A.D.

Avicenna, whose original name was Abu 'Ali al-Husain ibn 'Abdullah ibn Sina, was born 980 A.D. Unusually intelligent, he became a physician at the age of 17, when he was attached to the Samani court of the Sultan of Bukhara. He wrote philosophy and poetry as well.

From the early centuries until the pre-Renaissance period, when church dogma was dominant, portrait painters were not held in high esteem. Also, persons portrayed, however distinguished they may have been, were even more lightly regarded. It is small wonder, therefore, that in order to gain acceptance early portrait painters selected politically powerful or militarily important figures and presented them against or within religious backgrounds. Since the church controlled art and art forms, artists had to serve religion, and they could secure patronage only if the piety of their representations were acceptable. The break with this tradition was made in the fourteenth century by the early Renaissance masters. This break took two forms: The artists started to paint portraits of individuals rather than of groups, and they presented their subjects in fullface, thus emancipating themselves from the pre-Leonardo masters who were essentially profilists in the tradition of Greco-Roman, Minoan and Egyptian reliefs. This released a potential of greater expression and emphatic communication.

The humanism of the Renaissance marked an important transition in portraiture from the fifteenth to the sixteenth century. One of the characteristics in the development of portraiture in this period is that as evolution and refinement occurred, there was less dependence on background and greater emphasis on the face and thereby on the personality of the individual.

But even in the Baroque period, which was characterized by all sorts of outward symbols, great portrait artists were distinguished from their second-rate colleagues by an ability to realize on canvas the character of their objects. This ability was best expressed, for example, by portraying kings without depending on the scepter or crown as part of the portrait or by painting physicians without the symbol of Aesculapius.

From ancient times the doctor, the healer, has occupied an unusual place in the life of his community. He was often regarded as the priest who represented God on earth. He was worshipped and adored; people have prayed to him, and have made material and mental sacrifices before him. The doctor has been expected to bring health and to conquer disease, to protect and to deliver, to give advice and to guide. In the history of many cultures and religions, we see him pictured as the all-powerful, benign father-protector.

Doctors' portraits have played an important role in the history of the art. The first medical portrait known is that of Imhotep (circa 3000 B.C.), the distinguished physician of Pharaoh Zoser. Although mythology has made of this physician, priest, architect and statesman a supernatural being, his portrait is strictly that of a human being, with kind, almost primitive facial features.

Although the great philosopher-physicians of the classic Greek period lived in the times of greatest achievements in the arts, contemporary portraits are hardly known. There are no original portraits of Hippocrates or of Herophilus or Diocles, nor is it known whether any were ever created.

The classic Roman portrait is mainly given to us in the form of sculpture, but in a wall painting of Pompeii, the physician Yaphyx is shown treating the wounded Aeneas. Portraits of Avicenna are also later idealizations of the great physician of the Near East.

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NUTRITIONAL ANEMIAS

With the great stimulus to study the anemias, initiated by the work for which Whipple, Minot, Murphy and Cohn received worldwide acclaim, much research has been done on the mechanism of formation of the various constituents of blood. Anemias of many kinds have been classified. Deficiencies of erythrocytes, leukocytes, platelets, hemoglobin, gamma globulin and even individual chemical substances have been recognized. Some anemias, known to develop as a result of insufficient intake in the diet of materials necessary for normal formation of blood, are called nutritional anemias. Among these materials are vitamin B_{12}, folic acid, iron, pyridoxine and, possibly, others.

Dr. M. Rachmilewitz, Hadassah University Hospital, Jerusalem, has compared the incidence of nutritional anemia in pregnant women in Israel and in Burma. He found that nutritional anemia develops more often in women of childbearing age than in other women, since repeated pregnancies deplete the mother's store of blood-forming substances needed for fetal growth. A high prevalence of anemias of pregnancy was found in Israel; the incidence was even higher in Burma.

In these studies, recently established biochemical and microbiologic methods were used to determine quantitatively the amounts of the substances concerned in maternal and fetal blood and in various tissues of the body. The nutritional anemia of pregnancy was found to be due most frequently to combined deficiencies of iron, vitamin B_{12} and folic acid.

Most American physicians are aware of the decisions of the Food and Drug Administration concerning amounts of folic acid permissible in formulas that combine necessary vitamins and minerals in a single pill or capsule. Folic acid is not a toxic substance; however, its presence stimulates blood-forming organs so as to conceal vitamin B_{12} deficiency and permit the development of disturbances of the nervous system that are not present in anemias when the supply of vitamin B_{12} is adequate.

MORRIS FISHBEIN

AMEBIC HEPATITIS

Amebic hepatitis is known throughout the world as a condition which produces abscesses of the liver, sometimes single, sometimes (and

perhaps more often) multiple. However, cases of chronic amebic hepatitis without abscess were apparently, until recently, unknown. Dr. T. Doxiades, director, First Medical Clinic, Evangelismos Hospital, Athens, Greece, and his associates[1] have described what appears to be the first case of chronic diffuse non-suppurative amebic hepatitis.

A 32 year old woman who had pain on the right side of the thorax and a low fever reported that she had had periodic episodes of abdominal distress, distention, generalized abdominal pain, and diarrhea with blood and mucus in the stools since early childhood. A complete study, including all the usual laboratory investigations, showed enlargement of the liver, which was tender on palpation. Examination of stools for parasites gave negative results. Attempts were made to procure improvement with streptomycin. Then chloroquine was tried, but the patient's condition continued to deteriorate. Thereafter, emetine was given subcutaneously, with improvement four days later, disappearance of fever, lessening of pain, and reduction in the size of the liver. After eight days' intermission, the treatment was repeated for four days and the patient discharged as cured.

Four and a half months later, the patient returned because of recurrence of symptoms. At this time, abdominal puncture yielded a fluid which contained *Entamoeba histolytica.* Liver biopsy and ascitic fluid injected into animals also showed *E. histolytica.* The patient improved greatly with a high-calorie diet and antiamebic therapy. Nevertheless, after some weeks the liver was found still to contain amebae. Three months after the second admission, specimens taken from both lobes of the liver on exploratory operation were found to contain amebae, but there was no evidence of necrosis or abscess.

MORRIS FISHBEIN

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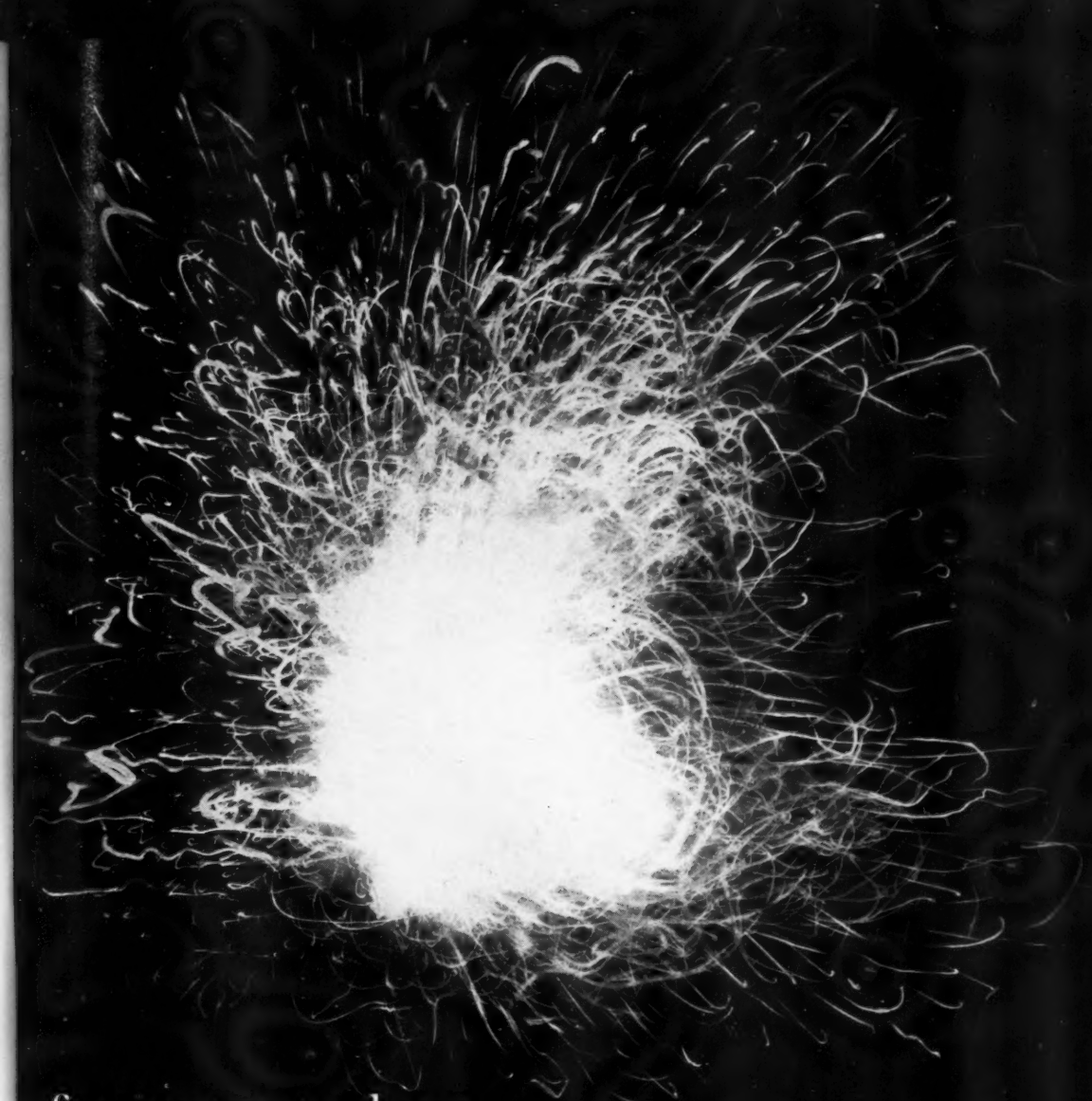
THE RHEUMATOID HAND

For many years the view prevailed that the crippling deformities of rheumatoid arthritis, which produce grotesque distortions of the fingers, offered little hope for repair and rehabilitation. More recently, an entire session of the International European Congress of Hand Surgery has been devoted to this subject, and instructional courses about such disturbances are included in the curriculum of the American Academy of Orthopaedic Surgeons. These inflammations involve the tendons, the muscles, the tissues around the joints, the joints themselves, and even the skin.

In the *Lancet,* Dr. Adrian E. Flatt, of University Hospitals, Iowa City, Iowa, has called attention to the application of orthopedic principles for the prevention and repair of disabled joints. The procedures include synovectomy with excision of diseased tissue, transposition of tendons, relief of edema and swelling, and maintenance of mobility. Each case must be studied individually. In some instances, the articular surfaces of the joints may be excised, and a prosthesis has been developed which is applicable in some cases. Splinting, physical therapy, and the prescription of specific drugs all may be helpful. Dr. Flatt concludes: "Current work, as yet unpublished, has revived interest in this therapy, and trials of newer similar compounds are in progress. But present knowledge of the natural history of the disease justifies the early use of prophylactic surgery. Of particular value is the excision of diseased synovium from joints and tendons before irreversible changes have taken place. Unfortunately, most patients are seen far too late for prophylaxis, and the measures outlined above can only be used in the hope of salvaging some function. No doubt, drugs rather than the scalpel will ultimately conquer rheumatoid disease, but meanwhile there is no reason to withhold proven [*sic*] surgical procedures from the many patients who are becoming steadily more crippled as their disease progresses."

MORRIS FISHBEIN



for patent ulcer...
to relieve tensions and to inhibit
hypermotility and hypersecretion

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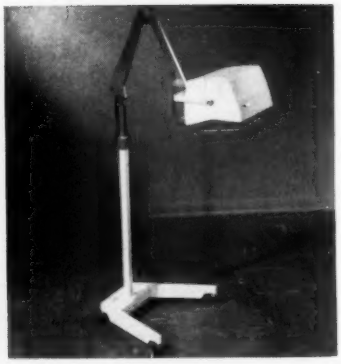
PATHIBAMATE-400 (full meprobamate effect)—1 tablet t.i.d. at mealtime, and 2 tablets at bedtime · PATHIBAMATE-200 (limited meprobamate effect)—1 or 2 tablets t.i.d. at mealtime, and 2 tablets at bedtime · Adjust to patient response. Each Pathibamate-200 tablet contains: PATHILON, 25 mg.; meprobamate, 200 mg. Pathibamate-400 tablets contain 400 mg. meprobamate.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.



• ZOALITE 500 INFRARED LAMP

DESCRIPTION: Featuring an improved quartz infrared tube with ideal spectral characteristics, this lamp supplies radiant energy capable of maximal tissue penetration. A retractable extension arm permits positioning over the widest treatment table, and an Alzak aluminum reflector insures even radiation over the treatment area. The lamp is 60 in. high with the arm retracted and requires less than 3 sq. ft. of floor space.
PRODUCER: The Burdick Corporation, Milton, Wis.

• CONVERZYME

PURPOSE: To aid digestion.
COMPOSITION: Each tablet contains, in standardized form:

Cellulolytic enzyme	5 mg.
Proteolytic enzyme	10 mg.
Amylolytic enzyme	30 mg.
Lipolytic enzyme	800 Ascher units

DOSAGE AND ADMINISTRATION: 1 or 2 tablets, swallowed whole, with or immediately after meals.
HOW SUPPLIED: Bottles of 100 and 500.
PRODUCER: B. F. Ascher & Company, Kansas City, Mo.

• VI-PENTA® ZESTABS

PURPOSE: Vitamin therapy.
COMPOSITION: Each chewable tablet contains 11 vitamins.
DOSAGE AND ADMINISTRATION: 1 Zestab daily.
HOW SUPPLIED: Bottles of 30 and 100.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

• ENDURONYL® AND ENDURONYL FORTE

PURPOSE: To treat hypertension.
COMPOSITION: Each Enduronyl tablet contains 5 mg. methyclothiazide (ENDURON®) and 0.25 mg. deserpidine (HARMONYL®). Each Enduronyl Forte tablet contains 5 mg. methyclothiazide and 0.5 mg. deserpidine.
CAUTION: Contraindications for and precautions in the use of Enduronyl are supplied with the product.
DOSAGE AND ADMINISTRATION: For mild to moderate hypertension, ½ to 1 tablet daily of Enduronyl initially, with adjustment of dosage after 10 to 14 days if necessary. For moderate to severe hypertension, up to 2 tablets of Enduronyl Forte daily.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: Abbott Laboratories, North Chicago.

• METHATAR CREME, METHAPHOR OINTMENT AND METHASEPTIC POWDER

PURPOSE: Topical treatment of allergic and inflammatory dermatoses.
COMPOSITION: Methatar Creme and Methaphor Ointment are amino acid-antiseptic formulations. All three products have a water-washable cream base.
HOW SUPPLIED: Methatar Creme and Methaphor Ointment, 1½ oz. tubes; Methaseptic Powder, packages of 12 envelopes, each envelope making 1 pt. of solution.
PRODUCER: Borden Company, Pharmaceutical Division, New York.

(Continued on page 110)

restful sleep, refreshed awakening

This is the promise of Noludar 300... a night of deep, refreshing sleep without risk of habituation or toxicity... 6 to 8 hours of undisturbed rest... an easy awakening in the morning, free of fogginess or barbiturate "hangover." Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are she'll tell you

"I slept like a log"

NOLUDAR® 300

brand of methyprylon

300-mg capsules

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

• CONDUCTION SYSTEM LOCATOR

DESCRIPTION: Used to determine the precise location of vital heart tissue (the bundle of His) during open heart surgery, this instrument consists of an autoclavable, electronic depth probe with triaxial gold electrodes affixed to a tone box. When the probe is passed over the ventricular septum, the tone changes pitch as the bundle of His is contacted; it can be located with an accuracy of 1 mm. and to a depth of 4 mm. A meter on the tone box also indicates changes in the relative conductance of the tissue. The instrument utilizes a transistor circuit and a rechargeable battery, and is equipped with earphones.
PRODUCER: Medtronic, Inc., Minneapolis.

• KANUMODIC®

PURPOSE: Symptomatic control of functional bowel syndrome.
COMPOSITION: Each timed-release tablet contains:

Pentobarbital	8 mg.
Methscopolamine nitrate	2 mg.
Cellulase (Dorase)	9.14 mg.
Pepsin N.F.	150 mg.
Glutamic acid hydrochloride	200 mg.
Ox bile extract	100 mg.
Pancreatin N.F.	500 mg.

CAUTION: This drug is contraindicated in glaucoma, in peptic ulcer, and in elderly patients with prostatic hypertrophy. Because it contains pentobarbital, it may be habit-forming.
DOSAGE AND ADMINISTRATION: 1 or 2 tablets, swallowed whole, with each meal.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Dorsey Laboratories, Lincoln.

• STUARTINIC®

PURPOSE: To treat iron-deficiency anemia.
COMPOSITION: Ferrous fumarate, vitamin B complex factors, desiccated liver and vitamin C.
DOSAGE AND ADMINISTRATION: 1 or 2 tablets daily, preferably after meals.
HOW SUPPLIED: Bottles of 100 and 500.
PRODUCER: The Stuart Company, Pasadena.

• REACTROL

PURPOSE: Antiallergenic therapy.
COMPOSITION: Each tablet contains 20 mg. clemizole hydrochloride.
HOW SUPPLIED: Bottles of 60.
PRODUCER: Tailby-Nason Company, Inc., New York.

• LE 60/40®

PURPOSE: Nutritional supplement for infants with borderline metabolic adequacy.
COMPOSITION: In powder form, this formula contains an electrolyte content reduced to that of human milk, a reduced total phosphorus load, a ratio of physiologic calcium to phosphorus of 2:1, a reversal of the cow's milk ratio of lactalbumin to casein to the human milk ratio of 60:40, and the essential vitamins.
CAUTION: This product is not recommended in any condition in which there is an abnormal loss of electrolytes.
HOW SUPPLIED: 1 lb. cans.
PRODUCER: Ross Laboratories, Columbus, Ohio.

• PATIENT TRANSPORTER

DESCRIPTION: Designed to serve as an admitting or transfer chair for moving patients from one area to another, this wheel chair is constructed without riveted joints. Frame and braces are of tubular steel plated in chromium. Standard equipment includes folding footrests, double ball-bearing swivel casters, rear wheels of nonmarking rubber, safety lock brakes, luggage rack, and a woven plastic covering.
PRODUCER: The Colson Corporation, Chicago.

• AMERICAINE® SUPPOSITORIES
(New Product Form)

DESCRIPTION: This topical anesthetic is now available in suppository form in boxes of 12.
PRODUCER: Arnar-Stone Laboratories, Inc., Mount Prospect, Ill.

restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinylhydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*

Great Names in American Medical History

Vermont

Charles S. Caverly, M.D.

This is one of a series of biographic sketches of outstanding physicians of the past from each of the 50 states. The subjects have been selected by the medical society of each state or its designated committee.

DR. Charles S. Caverly was one of the first physicians in the United States to identify poliomyelitis. He was born in Troy, New Hampshire, September 30, 1856, and prepared for college at Kimball Union Academy in Meriden, New Hampshire. In 1878 he graduated, Phi Beta Kappa, from Dartmouth College. He received his M.D. degree in 1881 from the University of Vermont College of Medicine, where he was class leader and was awarded three prizes. Later he did graduate work for 18 months at the Columbia University College of Physicians and Surgeons in New York, and then began practice in Rutland, Vermont, in 1883. He became a member of the Vermont State Board of Health in 1890 and its president in 1891. He was also professor of hygiene and preventive medicine at the University of Vermont College of Medicine, from which he later received the honorary degree of Sc.D. because of distinguished service in public health. He died in 1918.

In 1894 he published reports of an epidemic of poliomyelitis which occurred in Vermont. This report was considered to be the best contribution, at least in the United States, to knowledge of poliomyelitis up to that time. Dr. Caverly then published his studies of poliomyelitis in the *Journal of the American Medical Association* in 1896. He continued his interest in this disease, publishing articles in the bulletin of the Vermont State Board of Health in 1912, 1914 and 1916, at which time he recommended quarantine because of the communicable character of the disease. So serious was the situation for children left crippled by the great epidemic of 1914 that Dr. Caverly, through his own efforts and the generosity of an anonymous friend, established a special fund for the study of the cause and treatment of this disease. The Caverly Preventorium in Vermont bears his name.

YOUR FINANCES

FINANCIAL PLANNING FOR THE MEDICAL PRACTITIONER

Real estate for the neophyte . . . opportunities open to the investor for participation in real estate income and capital appreciation.

prepared by

CEDRIC CAMPBELL

for

Postgraduate Medicine

October 1961

REAL ESTATE OWNERSHIP satisfies a deep-rooted and probably primitive desire to own a tangible asset which has a high degree of stability and permanency. The landowner has long been regarded as a man of substance.

Emotions aside, land ownership has traditionally provided substantial income to many, has been the foundation of family wealth that has transcended generations, and even today continues to reward its owners, frequently quite handsomely.

A RECENT COMPARISON OF AVERAGE YIELDS from various forms of investments showed mutual funds earning 3-5%, common stocks returning 3-7% and real estate yielding 7-12%.

But there is one thing that real estate investments have in common with all other forms: risks. And here again only knowledge and information can help you avoid the pitfalls. Both the neophyte and the investor who has dabbled in real estate should profit from a review of some fundamentals before they add a commitment in real estate to their portfolios.

* * * * *

CURRENT TRENDS are focusing more attention on investments in real estate because of—

—High Yields on Investment.
—Tax-Sheltered Capital Appreciation.
—Long-Term Inflationary Indications.
—Continuing Population Explosion.
—Urban Renewal Programs.
—Increased Opportunities for Participation.
—Tendency of Common Stocks To Be Overpriced.

* * * * *

1. MORE FOR THE MONEY. While an investment in stocks or bonds yielding 4-7% may be viewed as unusually attractive, returns of 5% and more than 10% are not uncommon in real estate. (Of course, other factors such as liquidity of holding and long-term growth are factors to be considered when comparing two forms of investments. The comparison here is made to illustrate income alone.)

2. MORE MONEY TO KEEP. Tax-sheltered income appeals to most investors—particularly those in higher income tax brackets. Your tax shelter will vary with the form of participation in real estate you choose.

For example, if you own a share of a syndication, you will claim a proportionate share of the depreciation allowed on the property. Depreciation is figured on a sliding scale: greater allowance in the first years, less in the future. The portion of income received as depreciation will be exempt from federal and most state income taxes.

3. PROTECTING THE PURCHASING POWER OF YOUR DOLLARS. The long-term inflationary sweep shows little sign of reversing its trend, eroding the purchasing power of the dollar as it goes. Current world events and government spending commitments certainly provide no deterrents. And the lesson learned personally by millions of homeowners in the last 15 years is that real estate property will appreciate handsomely in extended inflationary periods. By extension, an investment in real estate at this point would seem to be an effective means of protecting capital against further deterioration.

4. GROWING POPULATION = GROWING DEMAND FOR AVAILABLE FARM LAND/HOMES/OFFICES/FACTORIES/RECREATIONAL FACILITIES. According to the 1960 census, population in the U. S. topped 179 million, an increase of 18.5% since 1950. Projected into the next decade, the population is expected to continue—and perhaps exceed—this rate of growth. Articles in periodicals and discussions on TV and radio conjure up visions of a radically shrinking per capita allowance of space. Even if a cataclysmic squeeze is far in the future, the inexorable increase of demand (with a very constant supply) spells out a moral for the investor.

5. URBAN RENEWAL: RENAISSANCE OF CITIES. Broad-scope programs of revitalizing deteriorating urban areas have been undertaken by investment groups as well as by city, state and federal government agencies. Affected will be not only those areas directly involved but also contiguous neighborhoods and, conceivably, entire cities, sparked into renovations and new construction. This chain reaction can produce broad appreciation of real estate values: good capital gains for investors willing to run the risk of misjudging where and when the rise in values will take place.

6. "YOU PAYS YOUR MONEY AND YOU TAKES YOUR CHOICE." It is now possible for any investor, no matter how limited his resources, to choose a form of participation in real estate from a wide array.

—Direct Purchase of Property requires the commitment of larger sums. The investor goes it alone, owning the property involved in the same manner that he owns his home (subject to mortgages and the full risks of ownership). The assistance of a reliable real estate broker, attorney or a successful real estate operator—particularly one who is familiar with property in the specific area of interest—is highly desirable. A good banking contact to obtain the best financing terms

is almost a "must." The property is most commonly a smaller housing unit, farm-land or commercial or industrial building or tract.

If at first glance the property appears to return an excellent 10, 12 or 15%, remember to deduct from rental income the depreciation allowances, insurance, taxes, assessments, repairs and maintenance, interest on mortgages and any other costs of ownership that may apply.

In the case of a bigger holding, appointment of a reputable real estate management firm is prudent for all but the most experienced real estate operator. The larger property may include additional expenses for salaries of maintenance personnel, advertising, disposal of trash, pest extermination, etc.

If the success of your investment depends directly on the success of the business enterprise renting the property from you, bear in mind that you are in essence investing in the business itself. Investigate the business of the lessee as carefully as you analyze the property itself.

—Direct Purchase of Mortgages may involve buying a first or second mortgage from a bank, savings and loan association, insurance company, mortgage placement agency, or directly from the property owner. The yield here will vary from about 5¼% to 10%, ranging from FHA-insured mortgages to mortgages offered on property in such rapidly growing areas as Florida. The investor assumes ownership of the mortgage and with it all the risks this position entails. Personal examination of the property, coupled with expert guidance, will lead the investor to a sound commitment and a satisfactory return.

> Availability to the individual of mortgages insured by the Federal Housing Authority is a recent development. These may be obtained from a mortgage agent (their ads are found in the business pages of metropolitan newspapers), from banks and savings and loan associations. Minimum sums of $10,000 are common. The investment is self-liquidating, with both principal and interest being paid in monthly checks, and a yield of 5¼% going to the investor.

—Participation in a Syndicate. Hundreds of thousands of investors have shared the benefits (and at times the disappointments) of participation in a real estate group. Where the syndication has been successful, the investor has purchased units of as little as $500 each and received 5-15% yield, a substantial portion of which was free from federal and, varying with location, state taxes. In addition, he probably watched his original investment appreciate over the years as property values rose and produced a neat capital gain over and above his return.

> The less fortunate investor found his yield reduced or wiped out when the property lost rental income. Wishing to liquidate his holding, he found no ready buyers for his shares—even when selling at a pronounced loss. In a smaller number of cases, the investor was chagrined to find he had been flatly defrauded out of hard-earned money.

For guidance in selecting a promising syndication, you might choose an interstate offering, which must conform to disclosure requirements of the S.E.C. Check thoroughly on the syndicating firm: Analyze the prospectus with your attorney, accountant or other knowledgeable expert.

—Investment in Real Estate-Oriented Stocks & Bonds. Some corporations have considerable holdings in real estate; others are engaged in real estate operations as a primary or secondary interest. The investor desiring both participation in real estate enterprises and the ease of buying and selling shares on the listed exchanges might consider stocks of some of these companies:

> Dole Corp., Georgia-Pacific, Lefcourt Realty, Minute Maid, Northern Pacific Railway, Rayonier, St. Regis Paper, Webb & Knapp.

—Shares in the New Real Estate Investment Trusts are the counterparts to mutual funds. They are government regulated, exempt from corporate taxes, and enjoy the higher yields usually found in real estate operations. Distributed income will be taxed at regular rates, distributed capital gains at long-term capital gains rates. While few of these trusts are currently available to the investor since enabling legislation was passed only last year, more are being formed in increasing numbers.

> According to the National Association of Real Estate Investment Trusts, this investment form has caught on in a big way. As of the beginning of July, 15 new trusts had filed with the S.E.C. Of these, the public stock offering as of July 5th was valued in excess of $33 million.

In addition, some conventional corporations are now considering reorganizing to conform to trust regulations. Some companies likely to make the switch could include Tishman Realty, Webb & Knapp, Uris Building, City Investing, and other similar corporations. Trusts already in operation include First Real Estate Investment Fund, Real Estate Investment Trust of America, and the Chicago Real Estate Trust.

As the number of trusts and shares increases, it is highly likely that mutual fund distributors will offer these shares and facilitate purchase by the average investor.

* * * * *

> IN THE NEXT ISSUE: Guaranteed Income With Minimum of Risk, which points the way to the place of the savings bank, savings and loan association and other outlets where money can be put to work with maximum safety.

* * * * *

Additional reading on material covered in this article might include: "Tax Shelter In Real Estate," William O. Casey, New York; "Real Estate Syndicator," published monthly; "The Valuation of Real Estate," Frederick M. Babcock, McGraw-Hill, New York; "How To Make Money In Real Estate," Stanley L. McMichael, Prentice-Hall, New York; "Real Estate Principles," Henry E. Hoagland, McGraw-Hill, New York.

Information contained in these articles is as accurate as careful checking and reliable sources can make it but cannot, of course, be guaranteed.

THE MEDICAL Bookman

► AN ATLAS OF ACQUIRED DISEASES OF THE HEART AND GREAT VESSELS

By Jesse E. Edwards, M.D., Professor of Pathology, Mayo Foundation, Rochester, Minnesota. Vols. 1, 2 and 3. 1,401 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $70.00.

Primarily directed toward pathologic cardiovascular findings, this atlas comprises a wealth of pathologic material, with one or more illustrations on each page. The illustrations are excellent in reproduction and subject matter. The author has cleverly correlated the pathologic observations with clinical findings. Where it is applicable he has used extensive cross-reference material, enabling one to use the atlas as a comprehensive reference text.

Dr. Edwards has utilized his wealth of experience in cardiovascular pathology to present a comprehensive study of the entire field. Common entities such as rheumatic carditis and valvular disease and less common findings such as Lutembacher's syndrome, embolism of the coronary artery, and various forms of tumors related to the cardiovascular system are adequately presented. The inclusion of such a broad spectrum of pathologic material could be achieved only through years of accumulated, extensive experience. Volume 1 is devoted to the diseases of the valves and pericardium; volume 2 deals with coronary arterial disease, hypertension, myocardiopathies, the heart and acute systemic disease, and cor pulmonale; and volume 3 presents pathologic problems in diseases of the great vessels.

These volumes should be of particular interest to the pathologist and cardiologist. The laudable economy of words will be popular with the busy practitioner and medical student. The extent and quality of the material and the manner of its presentation make this a worthwhile book for students, practitioners and academicians.

L. E. L.

► BLEEDING SYNDROMES
A Clinical Manual

By Oscar D. Ratnoff, M.D., Western Reserve University School of Medicine, Cleveland. American Lecture Series. 287 pages. 1960, Charles C Thomas, Springfield, Illinois. $8.50.

In the preface, Dr. Ratnoff states, "This book is a compilation of practical information about the clinical picture, pathogenesis, diagnosis and treatment of hemorrhagic disease, written for the practicing physician." In this he clearly outlines his purpose, and the result is a highly useful, well-written monograph for the clinician who otherwise may not have an opportunity to keep up to date in a quickly developing field.

The first chapter is a lucid presentation of the clotting mechanism as we know it today. The terminology, so characteristically confusing in this field, is discussed, and subsequently the author uses only the terms of his choice.

Presented as a series of interesting and informative essays on the various disorders of coagulation, this text will be a useful reference. The extensive, well-chosen bibliography will appeal to the internist with a special interest in hematology. The author draws freely on his own experience, but presents the various diseases in an impartial, unbiased manner. He avoids complicated technical information related to laboratory investigation of hematologic conditions.

R. W. H.

(Continued on page A-164)

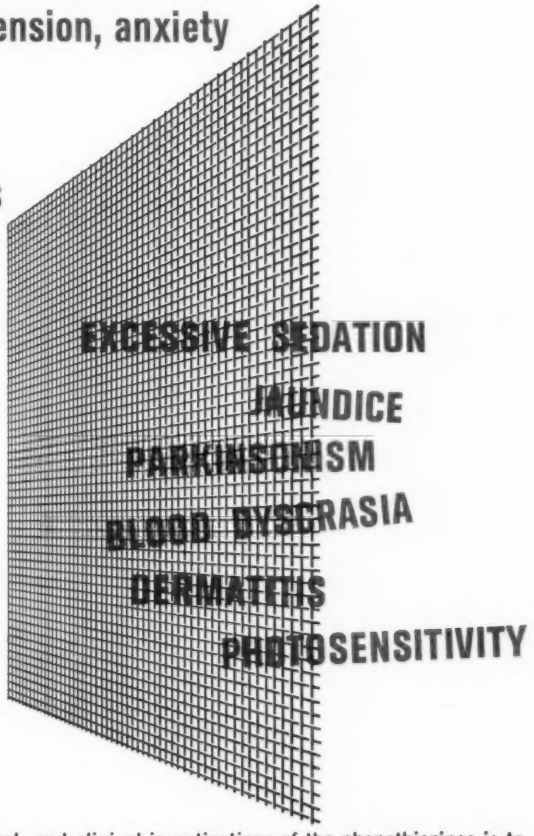
IN THE MENOPAUSE.

Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

and "screens out" certain side effects of tranquilizers, making it virtually free of:



"The aim of current chemical, pharmacological, and clinical investigations of the phenothiazines is to find derivatives possessing potent and selective tranquilization with a minimum of toxic action.... In agreement with the published results of other investigators, we believe that thioridazine [Mellaril] shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines."[1]

In the Menopause: A series of 150 menopausal patients were observed during Thioridazine (Mellaril) therapy for two years. Most patients had multiple complaints; the chief symptoms listed were: tension, insomnia, depression, fatigue and lethargy, irritability, chills, hot flashes and night sweats. The author states "The results were extremely good in those patients whose chief complaint was that of insomnia, tension, nervousness and, in general, the large group of menopausal symptoms that are due to disturbances of the psyche. The sense of 'well being' afforded these patients definitely decreased the intensity of 'hot flashes' and night sweats.... Eighty-five per cent of patients complaining of insomnia, nervousness and irritability received excellent relief."[2]

Mellaril is indicated for varying degrees of agitation, apprehension, and anxiety in both ambulatory and hospitalized patients.

Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d. Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily. Supply: Tablets, 10 mg., 25 mg., 50 mg., 100 mg.

1. David, N. A., Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a new phenothiazine, in the hospitalized patient, A.M. & C.T. 7:364, June 1960. 2. Caldwell, W. G.: Emotional Disorders in the Menopause and Treatment with Thioridazine, presented at Bahamas Conference on Internal Medicine, Nassau, Bahamas, April 30-May 6, 1961.

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SANDOZ

Authoritative advice on skin diseases of children from Morris Leider, M.D.

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PRACTICAL PEDIATRIC DERMATOLOGY

"What can it be?," "What is it called?," "What is its treatment?" and "What are its implications?" This new edition of Dr. Leider's popular book can answer virtually all of your questions regarding the practical and clinical management of skin diseases in infants and children encountered in normal daily practice. It is a synthesis of Dr. Leider's personal approach, well buttressed with sound theory. Coverage is complete, but the attention given a particular condition is governed by its frequency of occurrence.

This up-to-date new edition features more than 40 easy-to-use quick reference tables such as the "Annotated Formulary of 101 Useful Dermatologic Preparations for Topical Application." Moreover, it presents important new material on griseofulvin therapy of superficial fungous infections and a new highly effective therapy for plantar warts.

By MORRIS LEIDER, M.D. Published September 1961. 2nd Edition, 437 pages, 6¾" x 9¾", 280 photographs. 15 drawings. Price, $13.75.

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► A TEXTBOOK OF PATHOLOGY
An Introduction to Medicine

By William Boyd, M.D., Professor Emeritus of Pathology, University of Toronto Faculty of Medicine, Toronto, Ontario. Ed. 7. 1,370 pages with 792 illustrations and 20 color plates. 1961, Lea & Febiger, Philadelphia. $18.00.

Recognizing that morphologic manifestations of disease must be coupled with their functional meaning to give full expression to the potential of morphology, the author of this classic textbook has ably interwoven considerations of structural changes, disturbance of function, and the relation of lesions to symptoms. Moreover, this extensively revised and expanded edition covers recent advances in pathology, including immunity and hypersensitivity, derangements of body fluids, pigmentation, and ionizing radiation. The discussion of genetics has also been expanded.

Dr. Boyd's masterly use of the English language is legendary. This spark of genius serves to make his new edition not only pleasant to read but also clear and informative.

J. E. E.

► AN ATLAS OF PAIN PATTERNS

By L. A. Smith, M.D., N. A. Christensen, M.D., N. O. Hanson, M.D., D. E. Ralston, M.D., R. W. P. Achor, M.D., K. G. Berge, M.D., G. W. Morrow, Jr., M.D. and A. H. Bulbulian, D.D.S., Mayo Clinic and Mayo Foundation, Rochester, Minnesota. 54 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $12.50.

Covering the pain patterns that are associated with various forms of abdominal diseases, this atlas is an outgrowth of an exhibit entitled "Pain patterns and diagnoses of certain upper abdominal diseases," which was developed by a group at the Mayo Clinic. The atlas is well prepared; the illustrations are excellent, and the descriptions complete. The method of presenting the pain patterns, although not original, is novel, simple and easily understood. Variations in the pain patterns are colored in part and the clinical features of these patterns are emphasized.

No attempt has been made to make this volume complete or exhaustive; it merely represents certain general principles concerning the pain patterns in abdominal diseases. The material has been selected with care and ably presented, and it will prove particularly valuable for teaching purposes.

J. F. B.

(Continued on page A-167)

► THE HUMAN CEREBELLUM

By Jay B. Angevine, Jr., Ph.D., Associate in Anatomy, Harvard Medical School, Elliot L. Mancall, M.D., Assistant Professor of Neurology, Jefferson Medical College, Philadelphia, and Paul I. Yakovlev, M.D., Clinical Professor of Neuropathology, Harvard Medical School, Boston. 138 pages, illustrated. 1961, Little, Brown & Company, Boston. $15.00.

Until recent years the cerebellum has been of the nature of terra incognita, as illustrated by the tangle of anatomic terminologies used to describe its gross topography. This volume, which combines mature scholarship and the printer's art, begins with a lucid historical review of these multitudinous systems of nomenclature. In this section, beginning with Shilling's terminology (1864) and concluding with Larsell's recent one, each author's system is illustrated with a line drawing, clearly labeled to permit ready comparison with that of others. In the body of the text, Larsell's terminology is used, since the authors find it the most complete.

The bulk of the text consists of photographs of 42 serial sections of three normal cerebellums made in three different planes—sagittal, horizontal and coronal. The photographs have been enlarged to three times life-size. On the page facing each photograph is a line drawing made from a corresponding section stained for myelin.

This volume reflects the distinguished scholarship and meticulous skills of Dr. Yakovlev.

D. D.

► ESSENTIAL PATHOLOGY

By Roger D. Baker, M.D., Professor of Pathology, Duke University School of Medicine, Durham. 638 pages with 470 illustrations. 1961, The Williams & Wilkins Company, Baltimore. $9.50.

An accurate, clearly written reference work on pathologic states, this compact volume gives a concise portrayal of many of the innumerable disease conditions. Equal space is devoted to the pathologic states in general (inflammation, necrosis, lesions of metabolic origin, circulatory disturbances, chemical injury, infectious diseases, neoplasia, etc.) and to diseases of the various body systems.

The author's authoritative position in the field of infectious disease is reflected in his mature coverage of a subject which includes many exotic diseases.

J. E. E.

(Continued on page A-168)

Be Sure to Visit the **LEA & FEBIGER** *Exhibit at Booth 86*

Interstate Postgraduate Medical Association, Cleveland, Ohio, November 13-16, 1961

Wintrobe—Clinical Hematology
By MAXWELL M. WINTROBE, M.D., University of Utah, College of Medicine, Salt Lake City. *1186 pages, 7" x 10". 265 illustrations and 50 in color on 19 plates. New 5th edition. $18.50*

Boyd—A Textbook of Pathology
By WILLIAM BOYD, M.D., University of Alabama; Emeritus, University of Toronto. *1370 pages, 7" x 10". 792 illustrations and 20 plates in color. New 7th edition. $18.00.*

Silver—Radioisotopes in Clinical Practice
By SOLOMON SILVER, M.D., College of Physicians and Surgeons, Columbia University, New York. *New. Ready January, 1962.*

Behrendt—Diagnostic Tests in Infants and Children
By HANS BEHRENDT, M.D., New York City. *Illustrated. 117 tables. New 2nd edition. Ready January, 1962.*

Levinson and MacFate—Clinical Laboratory Diagnosis
By SAMUEL A. LEVINSON, M.D., Ph.D., University of Illinois Research and Educational Hospitals, Chicago; and ROBERT P. MacFATE, Ch.E., M.S., Ph.D., Board of Health, Chicago. *Approx. 1200 pages. 250 illustrations and 11 plates in color. More than 100 tables. New. 6th edition. Just Ready.*

Fleming, D'Alonzo and Zapp—Modern Occupational Medicine
Edited by A. J. FLEMING, M.D., F.A.C.P., and C. A. D'ALONZO, M.D., F.A.C.P., E. I. duPont de Nemours & Company. Associate Editor: J. A. ZAPP, Ph.D., E. I. duPont de Nemours & Company. *587 pages. 66 illustrations and 1 plate in color. 36 tables. New 2nd edition. $12.00.*

Soffer, Dorfman and Gabrilove—The Human Adrenal Gland
By LOUIS J. SOFFER, M.D., F.A.C.P., State University of New York College of Medicine in New York City; RALPH I. DORFMAN, Ph.D., Boston University Graduate School; and J. LESTER GABRILOVE, M.D., F.A.C.P., State University of New York College of Medicine in New York City. *591 pages. 79 illustrations and 1 plate in color. 20 tables. New. $18.50.*

Epstein—The Spine
A Radiological Text and Atlas. By BERNARD S. EPSTEIN, M.D., Albert Einstein College of Medicine, Yeshiva University, New York. *About 550 pages, 7" x 10". 750 illustrations on 388 figs. New 2nd edition. Ready January, 1962.*

Hollander—Arthritis and Allied Conditions
8 Section Editors. 30 Contributing Editors. Edited by JOSEPH LEE HOLLANDER, M.D., School of Medicine, University of Pennsylvania. *1306 pages. 417 illus. 6th edition. $20.00.*

Loftus—Meaning and Methods of Diagnosis in Clinical Psychiatry
By THOMAS A. LOFTUS, M.D., Associate Professor of Clinical Psychiatry, The Jefferson Medical College, Philadelphia. *169 pages. New. $5.00.*

Moyer and Brest—Hypertension: Recent Advances
Edited by JOHN H. MOYER, M.D., and ALBERT N. BREST, M.D., Hahnemann Medical College and Hospital, Philadelphia. *Approx. 630 pages. Illustrated. New. Just Ready.*

Ferguson—Drug Therapy
By FRANK C. FERGUSON, JR., M.D., Professor of Pharmacology and Chairman of the Department of Pharmacology, The Albany Medical College of Union University, Albany, New York. *About 400 pages. New. Ready January, 1962.*

Washington Square **LEA & FEBIGER** *Philadelphia 6, Pa.*

► THE CLOSED TREATMENT OF COMMON FRACTURES

By John Charnley, F.R.C.S., Orthopaedic Surgeon, Manchester Royal Infirmary, Manchester, England. Ed. 3. 272 pages, illustrated. 1961, The Williams & Wilkins Company, Baltimore. $10.00.

The first and second editions of this interesting text met with great success. The author's purpose was to impress the resident casualty surgeon with the commonplace fractures, the salient features of their treatment, and the advisability of and pitfalls in conservative management.

Even though this volume contains information which may be more applicable to the resident physician's work in the emergency room, it supplies stimulating reading for the orthopedic surgeon who has cared for fractures for many years. The author emphasizes the differences between closed and operative treatment of fractures and devotes many pages to the development of this long-persisting argument. He emphasizes that conservative management of fractures may not be successful in all instances, but points out that when it is unsuccessful the effects and complications are not as serious as those accompanying operative intervention of some fractures. He also comments on the mechanics of conservative management of fractures, and the book is profusely illustrated with amazingly clear line drawings of the vectors and forces used in such conservative management. The plaster technic and fractures which can be treated best by plaster immobilization are emphasized.

Both roentgenographic and diagrammatic illustrations are informative and instructive, comprising an integral part of the educational value of the text. In short, this edition should be received as successfully as the previous two, and will serve to enhance further Dr. Charnley's reputation as a clear thinker and an educator.

E. W. J.

Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Listings appear on pages 310 and 338.

RICHARD ARMOUR

JUST WHAT THE DOCTOR ORDERED

There will be an Institute on Health Care Needs of the Elderly Patient at the Hotel Chamberlin, Old Point Comfort, Virginia.—*Medical News.*

If such an institute must meet
For geriatric biz,
What place so fitting, so complete,
As Old Point Comfort is?

We like the Old, we like the Point,
And do not mean to jest
In saying that, at such a joint,
We like the Comfort best.

Perhaps, though, when the meeting's done,
Physicians taking care
Of old folks will, then, one by one,
Send aged patients there.

ONE GOOD TOURNIQUET DESERVES ANOTHER

The indiscriminate use of tourniquets, according to a professor at the University of Louisville School of Medicine, can be damaging.—*News item.*

Beware the misused tourniquet
That stops the blood from flowing.
It should be placed precisely when
And where, by one who's knowing.

A tourniquet should not be used
Just any time and place.
A pressure dressing may be best,
For instance on the face.

A patient with a nosebleed, say,
May wind up quite a wreck
If there's a tourniquet applied,
And tight, around the neck.

Schering

"The experience to date with griseofulvin has been so promising for the management of *Microsporum audouini, Trichophyton tonsurans* and *Trichophyton violaceum* that it has become the treatment of choice for these infections of the scalp."[1]

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Supplied: FULVICIN Tablets (scored), 500 mg., in bottles of 20 and 100; 250 mg., in bottles of 30, 100 and 500. *Reference:* Sulzberger, M. B., *et al.:* Dermatology: Diagnosis and Treatment, ed. 2, Chicago, Year Book Publishers, 1961, p. 350. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

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***Tinea capitis due to* T. tonsurans *cleared after 7 weeks of therapy with* FULVICIN.**

FROM WEINER, M. A.; GOULD, A. N., AND GANT, J. O., JR.: GRISEOFULVIN IN RINGWORM INFECTIONS. SCIENTIFIC EXHIBIT PRESENTED AT A.M.A. CLINICAL MEETING, DECEMBER, 1960, WASHINGTON, D. C.

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Aug. 1—Lay late and then to the main street to view Turkish glass and make some purchases. In the afternoon to Üsküdar, made famous by Eartha Kitt, and saw the living of the population in suburban Istanbul. After tea on the terrace came Harold and Sally Neher and Drs. Urgancioglu and Akcasus with the ladies, and we dined in the Sirdarvan.

Aug. 2—In the morning to buy textiles along the main street, and then to the bazaar. In the afternoon to visit Mr. Adler, our friend in the Hilton. Next to the steamship Kriti, and dined sumptuously on board to a musical departure in the magic of the Bosporus at night.

Aug. 3—At noon disembarking at Dekelia and by buses to Pergamum. Here seeing the palaces; market place; the temples to Athena, Isis and Serapis; and the remains of the great temple of healing. In the evening back to the Kriti, meeting on board the opera singer Madame Resnick and Dr. Esther Goldstein Miller of Boston.

Aug. 4—This day the Kriti halts at Kusadasi and all go to see the temple of Artemis (Diana), one of the Seven Wonders of the World. Next, to the top of the mountain to see the home to which the Virgin Mary went after the Crucifixion. Then visited the Basilica of Saint John.

After lunch to Paros, and by mule-back to visit its monastery; then to see the Grotto of Saint John the Divine. Back on the Kriti meeting the McNutts from Tehran and Dr. Robert Hand and his family from Halifax, and we talked while the Kriti sailed on the Aegean Sea.

Aug. 5—Early at Rhodes to visit the magnificent City of the Knights of Saint John, the Castello of the Master, the shops of Rhodes, the temple of Apollo, and the stadium. In the afternoon by bus to Lindos, another ancient city, with an acropolis overlooking the bluest sea these old eyes have ever seen.

Aug. 6—In Crete visiting the Minoan Palace at Knossos of 4000 B.C. Then to the great museum where are the frescoes, bathtubs, tombs, jewelry and relics of hieroglyphics and lineal writing.

In the afternoon stopping at Santorin, where the city of Phira perches precariously 1000 ft. up on a volcanic rock, while the ship floats in the crater of an extinct volcano. And here old Pepys decided the pleasures of climbing aboard a donkey are not sufficient attraction to make the performance a repetitious one. A young man protested bitterly to his father, "If I have to look at any more rocks, I'll kill myself." Next, a gala dinner and farewell to our friends and this tour of the Grecian islands.

Aug. 7—The Kriti docks at Piraeus, and we depart for the air-conditioned Grand Bretagne in Athens. At noon to luncheon came Nick Photinopoulos. In the afternoon a siesta, because of the great heat, and in the evening to dine at the shore on fish. Then to see folk dancing in the open-air theater in Piraeus.

Aug. 8—Writing and dictating, and in the afternoon among the shops. In the evening to the ancient open-air theater at the Acropolis to hear the Halle Orchestra of Manchester, England, led by Sir John Barbirolli. Thereafter to dine in a typical Greek tavern.

Aug. 9—To the National Museum to see the Minoan relics, the statues of Aesculapius, the votive offerings, the masks of gold, and other treasures. In the afternoon to the Benaki Museum, and then to the display rooms of Saridis to see modern furniture designed by T. H. Robsjohn-Gibbings from ancient Greek, Etruscan and Roman models. In the evening again to hear the Halle Orchestra with Isaac Stern, after which with Nick Photinopoulos to Floca's for dinner.

Aug. 10—With Anastasius Dontas to visit Ben Jackson, director of information for the United States in Athens, and discussed problems of the information centers. Then to the Queen Alexandra Hospital, with 600 beds and an enormous obstetric service with 30 deliveries per day. Here, modern medicine is practiced under Drs. Louros and Malamos. Young residents here have worked in many American centers. Under research grants from the NIH, many projects are under way with isotopes and electronic devices. The delivery rooms are up to the minute, and every gynecologic patient has cytologic study.

At noon to lunch with Dr. Doxiades of the Evangelismos Hospital and Dr. Manos, a surgeon who worked in Rochester, Minnesota, in the 1930s. Dr. Doxiades does research especially on chronic diffuse nonsuppurative amebic hepatitis. So after a siesta to drive to Cape Sounion on the bay beyond the airport.

Aug. 11—All this day on a bus tour to Corinth, Nauplia, Epidaurus and Mycenae. Here met the Katers from Australia and the Drs. Samshin from Michael Reese Hospital, Chicago.

Aug. 12—At noon lunching in the Grand Bretagne with Anastasius and Genie Dontas and saw its owner, M. Petrakopoulos. In the evening with Nick Photinopoulos driving to Kifissias to visit the Dontases, and then dining at the Blue Pines next to a fountain surrounded by fragrant trees.

Aug. 13—Rested, wrote and packed, and to the airport to fly on Olympic Airways to Israel. At the Lydda airport met by M. Landau, president of the Israel Medical Association; Sussman Muntner, noted medical historian; and Rabbi M. Elefant, in charge of the Maimonides project (a complete translation of his medical works in English and modern Hebrew). So to the new Sheraton Hotel in Tel Aviv.

Aug. 14—Until noon catching up with the mail and then driving to Jerusalem along 40 miles of road paralleling the Jordan border. Saw two Arab villages, a castle left from the Crusades, and the birthplace of the prophet Samuel. To the headquarters of the medical association, where the delegates assembled to hear the report of Dr. Krieger and to memorialize M. Sherman, who founded this fellowship.

Next, to the home of Professor Muntner, viewing from the roof all of the city and Mt. Scopus and see-

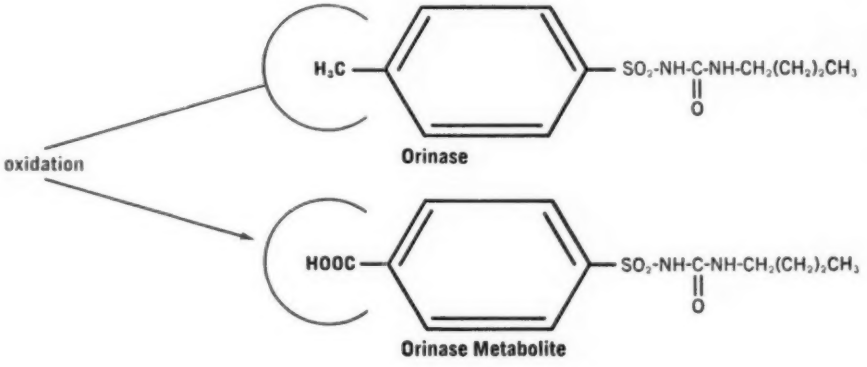
(Continued on page A-172)

Why is the methyl "governor" in Orinase so important?

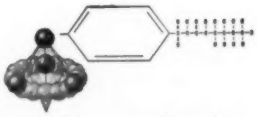
One of the most significant advantages of Orinase therapy is the rarity of associated hypoglycemic reactions.

This widely-reported clinical benefit is a function of the exclusive Orinase methyl "governor." Lending itself to ready oxidation (principally, it is thought, a hepatic process), the methyl group ensures prompt metabolic inactivation of the Orinase molecule. What actually happens is that a rapidly- and continuously-excreted carboxy-metabolite is produced that has no hypoglycemic activity at the existing levels.

As a result of the oxidation of its methyl group, Orinase shows a decline in activity soon after it reaches its effective peak in the plasma. Maintenance dosage serves to reduce blood sugar levels to normal, but rarely below that point, and there is no reported problem of accumulation.



Orinase*



An exclusive methyl "governor" minimizes hypoglycemia

Indications and effects: The clinical indication for Orinase is stable diabetes mellitus. Its use brings about the lowering of blood sugar, glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear.

Dosage: There is no fixed regimen for initiating Orinase therapy. A simple and effective method is as follows: *First day*—6 tablets; *second day*—4 tablets; *third day*—2 tablets. The daily dose is then adjusted—raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

Patients receiving insulin (less than 20 units)—discontinue insulin and institute Orinase; (20 to 40 units)—initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units)—reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed. In candidates for combined Orinase-insulin therapy, an individualized schedule is usually obtainable during a trial course of two or more weeks.

Contraindications and side effects: Orinase is contraindicated in patients having juvenile or growth-onset, unstable or brittle types of diabetes mellitus; history of diabetic coma, fever, severe trauma or gangrene.

Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of translation from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 650,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:
Tolbutamide ..... 0.5 Gm.

Supplied: In bottles of 50.

*Trademark, Reg. U.S. Pat. Off.—tolbutamide, Upjohn

June, 1961

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Upjohn

ing the bibliographic treasures, including the writings of Asaph and Maimonides. Thereafter to the opening meeting, with addresses by the officials, the president of the university, mayor, minister of health, the prime minister Ben-Gurion (who praised highly the Maimonides project), and Hermann Zondek and greetings by delegates from the United States, Argentina, France and England.

Aug. 15—The scientific sessions begin, with old Pepys presiding and reports of advanced research on blood groups in various races, hereditary disease and consanguineous marriages, favism and drug-induced hemolysis, genetic defects in various populations, hematology and new knowledge of migrations, and nutritional anemia. Speakers included from the university Professor Elisabeth Goldschmidt and D. Nelken, from the government hospital at Tel Hashomer Drs. A. Szeinberg, Bracha Ramot and Ch Sheba, and from the Hadassah Hospital the famous M. Rachmilewitz, who is dean of the medical school.

Next to visit the Hermann Zondeks, where came Dr. E. E. Lieber of London, and we had anecdotes of medical history and practice and a repast especially prepared by Dr. Gerda Zondek. Thereafter to visit the cemetery, the tombs of the members of the Sanhedrin and their families, and the new building which houses the Israel Torah Research Institute, given by Judge Abe Marovitz of Chicago in memory of his mother. The third floor is devoted to the research on Maimonides. All this was beautifully designed and decorated by Goldie Elefant. Then driving back rapidly to Tel Aviv to listen to the Israeli election returns.

Aug. 16—Driving along the Via Maris past Megiddo and Armageddon to Tiberias and the Sea of Galilee on the Jordan River. At Tiberias met Fathers Wheeler and Dinardo of St. Elizabeth's Hospital. Next, to the tomb of Maimonides and back to Tel Aviv by way of Affula.

Aug. 17—To the Weizmann Institute, seeing the research departments and interviewing the investigators in electronics, biochemistry, pharmacology and other fields. Here, talked with Anna Weizmann (sister of the founder) of amebicides and products derived from citrus peels; with Professor Katzier of polymers; and with Danon of electron microscopic studies of blood cells, their aging and development. With Dr. William Taub saw new devices for studying electroencephalography of cats and pigeons and for studying comparative pharmacology, and talked with Professors Berenblum and Sachs of work on carcinogenesis and leukemia. Then to luncheon with all the staff and received a copy of Ritchie Calder's work on the Institute and viewed the library.

So bade good-by to Frolenko of public relations and drove with Berman to Jerusalem. Here, Karpas proudly displayed the new, finely equipped Hadassah Hospital with some 600 beds. Then, to the home of Israel's president Ben-Zvi, who gave a fine reception, seeing there Berconsky from Argentina, Simon from Paris, Schaffer from Johannesburg, Diamant from Stockholm, and many Americans and Canadians. So with Bernhard Zondek to his home, and then by car back to Tel Aviv.

Aug. 18—In the lobby of the Sheraton, meeting Kosoll of Glencoe, with his wife and children. Also here was Sam Bellows, working on bonds. Then to walk among the shops and to the office of the *Jerusalem Post*. The day being exceedingly hot, next to a siesta, reading some short tales by Neil Bell, whose narratives move swiftly. This being Friday, the sound and the movement of the busy city suddenly cease and the restfulness of the Sabbath is all pervasive.

Aug. 19—A quiet Saturday playing "Scrabble" and reading until evening, when came the Katzenellenbogens, the Gombergs from Haifa, and the Elefants to dine and say au revoir.

Aug. 25—To the Leonardo da Vinci Airport, and there came Pietrogrande with his boy and girl. Then off to Vienna on Oestreichischer Airlines. In Vienna at the airport was M. Arthur Kline, and so to the Hotel Imperial.

In the afternoon to the American Medical Society of Vienna and here were Professors Fellinger, Chiari, Fuchsig and Novotny. Next, to the inn called The Third Man, and later Dr. Munib Shahid of Beirut joined us at Fellinger's home for coffee.

Aug. 26—Reading medical periodicals collected at the American Medical Society of Vienna and then walked the Kartnerstrasse to the beautiful shops, after which back to the scrivening. In the afternoon to the Staatspark to hear the band, and in the evening to the Alte Haus.

Aug. 27—Rested late reading and then to converse with the Okens from Chicago and the Winters from Newark about our respective travels. After luncheon visiting the rose gardens and to dinner came Kline and Annie Engel.

Aug. 28—Early to the Hofburg, where was the opening session of the European Congress on Hematology. Before a great audience spoke Fellinger; Alder from Switzerland; Hayek, dean of this school; and Mayor Jonas, minister of education. Thereafter to luncheon came the Horthys. Then off by plane to Amsterdam, where at the airport were Van Tongeren and son Philip. To the Amstel came Van Tongeren, Cauverien and Barton of Boston, en route to the Mental Health World Congress in Paris.

Aug. 30—With B. Van Tongeren to drive to Leiden, visiting the great new physiology department of Professor Duyff and with him to luncheon in an ancient restaurant. In the evening with Dr. Polak, Van Tongeren and all the ladies to the Hotel Europa, and we dined until late, with many fine anecdotes to enliven the farewell party.

Aug. 31—Early by car to Leiden and saw there the university. Then on to Delft to view the exhibits of china and the great antique show. Next, to Bonn, Germany, and to Godesberg to a new hotel where many diplomats stay.

His Classification

The patient was wheeled into the operating room, with the affected area anesthetized locally. He observed his surgeon fully uniformed, the resident, the anesthetist, and an intern taking notes.

"Looks like a business meeting," he said. "Dr. Gross is evidently chairman of the board, and Dr. Johnson is vice-chairman. That guy is the secretary! But what am I?"

"You," said Dr. Gross, "are chairman of the finance committee."

From the *Rotarian*

* * *